Sinus Headache, Migraine, and the Otolaryngologist

A Comprehensive Clinical Guide

Mark E. Mehle

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This book is dedicated to all the people who made this project possible. My parents, Rosemarie and Anthony who raised me with a respect for education; my brother, Anthony Mehle, M.D., who taught me a healthy disrespect for medical dogma; and my family, Barbara, Anna, and Jonathan who tolerated my absences and distractions over the years.

I would also like to thank my multiple coauthors who took time out of their busy practices to contribute to this volume. I know we all shared an enthusiasm for this topic and an understanding of its importance; your tolerance of my deadlines and editorial comments is much appreciated.

Finally, I would like to thank the many patients over the last 25 years who have come to me suffering from sinus headaches or other manifestations of migraine, and who expressed frustration with previous or ongoing misdiagnosis or mismanagement. If this book is a small step toward supporting a better appreciation of the diagnosis and management of this common but underappreciated problem, it will be well worth the effort.

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Chapter 1
Sinus Headache, Migraine, and the Otolaryngologist: An Introduction

Mark E. Mehle

In 2004 Schreiber et al. evaluated 2991 patients with a chief complaint of "sinus headache" and found that 88% of them satisfied the International Headache Society (IHS) criteria at the time for migraine or probable migraine headache. In this study they excluded patients who had evidence of infection (fever, purulent nasal discharge) but also excluded any of them who had a history of migraine. Although sponsored by a pharmaceutical company, this article confirmed what otolaryngologists and other physicians had long suspected: that primary headache disorders are common in "sinus headache" patients [1].

Now, over 10 years later, it is increasingly well recognized that migraineurs are part of the otolaryngology (ENT) and allergy patient populations [2, 3]. In general, migraine is incredibly common, with approximately 20% of women and 6% of men suffering the effects of this underlying disorder [4]. Many of these migraineurs remain unrecognized, despite efforts to promote migraine diagnosis in specialty practices as a sinus headache etiology [5, 6]. The migraine process is also recognized as an underlying cause of imbalance and vertigo, and this is increasingly appreciated as well. Migraine is the most common cause of vertigo presenting to ENT physicians, even more common that benign paroxysmal positional vertigo (BPPV) [7]. Clearly, migraine needs to be on the "differential diagnosis radar" for any otolaryngologist, regardless of the scope or focus of their practice.

Up to this point, there has been little focus on migraine diagnosis and treatment in otolaryngology and allergy residencies and fellowships. Many ENT practitioners profess ignorance of migraine management, even though many have gained

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Table 1.1 The diagnostic criteria for migraine [8]

Migraine without aura
A. At least 5 attacks fulfilling criteria B–D
B. Headache attacks lasting 4–72 h (untreated or unsuccessfully treated)
C. Headache has at least 2 of the following characteristics:
1. Unilateral location
2. Pulsating quality
3. Moderate or severe pain intensity
4. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
D. During headache at least 1 of the following:
1. Nausea and/or vomiting
2. Photophobia and phonophobia
E. Not attributed to another disorder
Migraine with aura: If aura is present: At least 2 attacks fulfilling criterion B is sufficient for diagnosis

confidence in diagnosis. The IHS migraine diagnostic criteria (presented in Table 1.1) [8] are increasingly well known and utilized by otolaryngologists, and are likely to "capture" the diagnosis of migraine in most, but not all cases. These criteria remain a great place to start when a physician is learning about migraine.

Once a physician becomes proficient at diagnosing migraine, a second problem arises: a shockingly high number of people seem to have it! This is not unexpected considering the incidence cited above, but still can be quite surprising. This situation is similar to the greater appreciation of gastroesophageal or laryngopharyngeal reflux disease (GERD, LPR) that has arisen over the last 30 years. GERD and LPR are very common and have become a recognized source of globus/throat clearing symptoms. After a push to increase the recognition of these problems, the vast majority of ENT practitioners learned the medical management of these problems, and incorporated this treatment into their practices [9]. It is amazing to think that otolaryngologists in the 1960s and 1970s neither accurately recognized nor treated these patients.

The otolaryngologist GERD treatment practices stand in contrast to migraine, where many ENT physicians are reluctant to treat the disorder, citing a lack of training and information regarding migraine management, concerns about using unfamiliar medications, and confusion regarding appropriate patient workup. Considering that most primary care physicians are comfortable in this regard, it is time to reassess this stance.

The author has heard on several occasions that there is no clear and concise guide to treating these patients for ENT physicians; no "migraine handbook" exists for otolaryngologists or allergists. This volume is an attempt to rectify that situation.

This book is broken down into several chapters, many of which could easily stand on their own. A focus of attention has been placed on clinical practice, although the "mechanism" chapter—Chap. 2—also serves as a fascinating glimpse into the cutting edge of neural pathophysiology.

The chapters on diagnosis, workup, and management have been contributed by national experts in neurology and offer a thorough background in current diagnostic and treatment guidelines. Although migraine can present in a great variety of ways, most migraineurs can be classified as such once the diagnostic criteria (e.g., Table 1.1) are learned. It certainly helps the practitioner to know that the vast majority of patients presenting with headache have migraine [10], and a focus on recognizing this is a great diagnostic starting point.

The medical management of migraine is also an important step for the otolaryngologist. Just as an understanding of histamine receptor blockers and proton pump inhibitors (H2 blockers, PPI medications) became a standard part of ENT training and practice, one will find (at the least) that triptan medications should become part of our treatment armamentarium as well. Many of these medications are similar to oral decongestants in their complications and risks, and with a little education can be used safely in the majority of these patients [2]. Similarly, migraine preventative medications have become part of the modern ENT practice, particularly in the realm of neurotology, as discussed in Chap. 8. It would be disappointing, indeed, if the majority of otolaryngologists refused to treat *the most common cause of vertigo* in our practices, simply out a lack of training or understanding of the medications necessary to do so.

Many otolaryngologists, of course, prefer to involve our neurology colleagues early in the treatment process, but it is important to realize that not all neurologists have an interest in migraine. Neurology training may also be variable—not all gastroenterologists are well versed in the LPR presentation of GERD, and not all neurologists understand vestibular migraine or sinus headache complaints. A good working relationship with a headache-focused neurologist can be crucial in patient management [11]. Regardless, a thorough understanding of medical migraine management is helpful for the otolaryngologist, as the effects and side effects of these treatments affect our mutual patients.

What about surgical intervention for these patients? As a surgical specialty, we often focus on our role as interventionalists for patients when medical management has proven disappointing. Botulinum toxin has been approved for the management of *chronic* migraine, and may already be available in ENT offices where it is used cosmetically. This may certainly allow an interested otolaryngologist to be involved in the management of these challenging patients, and Chap. 5 provides the necessary background information regarding this. ***Chronic migraine*** is defined in this context as more than fifteen headache days per month with headache lasting 4 hours a day or longer.

Sinus headache complaints are often the most troubling symptom for sinus surgery patients, and are also the symptoms most likely to persist after surgery. Otolaryngologists will often admit these “headache failure” discussions are a typical part of our informed consent discussion with patients, but only now are we starting to understand the nature of these failures. Migraine has become the cornerstone of our sinus headache/rhinogenic headache discussion [2, 3, 5, 6, 11].

Migraine and allergy have been found to be comorbid in several population studies. They certainly share common neural pathways as well as neurochemical

mediators (as well as a seasonal pattern), but a causal relationship has proved elusive. Could treating allergy help allergic migraineurs? Chapter 7 provides a thorough base of information to provide groundwork for further study into this intriguing area.

What about surgery performed deliberately for migraine? Chapter 10 provides a thorough discussion into this controversial area. The vast majority of the published information on this topic comes from the plastic surgery literature, and may have escaped the notice of the otolaryngologist. A review of the "placebo effect in surgery" section in Chap. 6 is recommended reading prior to Chap. 10. Should this be a part of an otolaryngology practice? The future may hold answers to that thus far unanswered question.

Chapter 9 provides an enlightening and perhaps sobering review of the extent in which migraine can affect our patients. Migraine is more pervasive than is generally realized in many common complaints that we see. This chapter provides an entertaining and certainly thoughtful review.

Finally, there is the global evaluation and management of the migraineur. Most ENT practitioners provide dietary and lifestyle recommendations for GERD patients—what about the migraineurs? It may come as a surprise to ENT physicians that there are well done, randomized, placebo-controlled studies regarding dietary, nutritional, and supplement management of these patients. Those of us who loathe unscientific management recommendations will enjoy the balanced and thorough treatment of these issues in Chap. 11.

The appendices are provided to show examples of patient education materials that can be provided to patients. In the author's experience many of these patients are desperate for reliable information, and the otolaryngologist or treating allergist can provide an important service in that regard.

In summary, migraine is already an important part of your practice, and appears in some form or other daily. Now is the time and opportunity for the otolaryngologist or allergist to appreciate that fact, and to acquire the necessary information to recognize and manage this common problem.

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Chapter 2
Anatomy and Pathophysiology of Migraine

Stewart J. Tepper

Introduction

The anatomy and the pathways in the pathophysiology of migraine, while extensively explored in the past several decades, remain not fully connected. Migraine is generally an inherited neurologic disorder, with both variable genetics and penetrance. The accepted wisdom is that a tendency to neuronal hyperexcitability is what is common to all forms. The onset of an attack of migraine, or the persistence of daily headache in chronic migraine, may be initiated in the brainstem or may begin peripherally in the meninges. The role of cortical activation preceding an attack is also debated.

Migraine is principally a neuronal disorder. Neurons activate the process. The consequence of the excitation can result in vascular, hormonal, and autonomic manifestations, but the initiation is likely neurological. The old idea that migraine was a vascular process has been replaced by the concepts of a neurovascular syndrome, predominantly neuronal.

In favor of a peripheral process at migraine onset are the discovery of neuronal pathways from scalp to dura and meninges to cortex, the inhibition in rats of cortical activation by botulinum toxin via Transient Receptor Potential Vanilloid type 1 (TRPV1) and Transient Receptor Potential cation channel, subfamily A, member 1 (TRPA1) receptors, and the profoundly effective migraine prevention seen rapidly with anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies (mABs) which do not cross the blood–brain barrier and therefore have only initial peripheral effects. In favor of a central process are the activation of central

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neuromodulatory pathways and nuclei found functionally in migraine, specifically in the dorsal pons.

The genesis of aura is activation of N-methyl-D-aspartate receptor (NMDA) glutamate receptors and cortical spreading depression or depolarization (CSD). The ability to suppress CSD is associated with acute and preventive effects by drugs and neuromodulation devices, but whether this suppression alone is sufficient for either clinical effect is unresolved.

Migraine pain is due to both meningeal vasodilation and neurogenic inflammation. Presynaptic release of CGRP, vasoactive intestinal peptide (VIP), substance P (SP), neurokinin A, and likely, pituitary adenylate cyclase activating polypeptide-38 (PACAP-38) results in these processes. Triptans and ergots prevent release of CGRP, reverse CGRP-induced vasodilation, and interfere with return of the pain signal from periphery to brainstem. Anti-CGRP drugs and biologics can terminate migraine acutely (gepants) or prevent migraine (monoclonal antibodies).

A trigemino-parasympathetic or trigeminal autonomic reflex arc involves efferents from the superior salivatory nucleus (SSN) synapsing in the sphenopalatine ganglion (SPG), and then post-synaptic neurons proceeding to sinus, ocular, and nasal organs. Activation of this reflex, which involves VIP, results in sinus-like symptoms or cranial autonomic symptoms and signs in migraine, and nociceptive afferents return signals to the brain via the first division of the trigeminal nerve or ophthalmic nerve. The exit of parasympathetic efferents via the SPG allows for targeting of this ganglion for acute and preventive treatment of migraine via blocks, ablation, or neuromodulation.

Pain Mechanisms and Anatomy

In the case of migraine, it may be reasonable to start with what is clearly known, and then work backwards. The pain mechanisms of migraine are peripheral, in the meninges. Presynaptic activation by serotonin 1_D (5-HT 1D) receptors results in the release of CGRP, VIP, substance P (SP), neurokinin A, and likely, PACAP-38 [1, 2].

These peptides are neuro-inflammatory, and at least two, CGRP and PACAP-38, vasodilate. Therefore, post-synaptic effects in the meninges include the activation of the arachidonic acid cascade with its attendant inflammation, and vasodilation. The inflammation also includes mast cell degranulation; the vasodilation is associated with vessel fenestration and further release of plasma peptides. These two mechanisms, neurogenic inflammation and vasodilation, stimulate nociceptive afferents which carry pain signals centrally on the first division of the trigeminal nerve, the ophthalmic nerve (V1) (Fig. 2.1).

The afferent limb of the trigeminal system has its cell body in the trigeminal ganglion and synapses centrally, in the upper spinal cord and brain stem, in the trigeminal nucleus caudalis (TNC). This complex was named the trigeminocervical

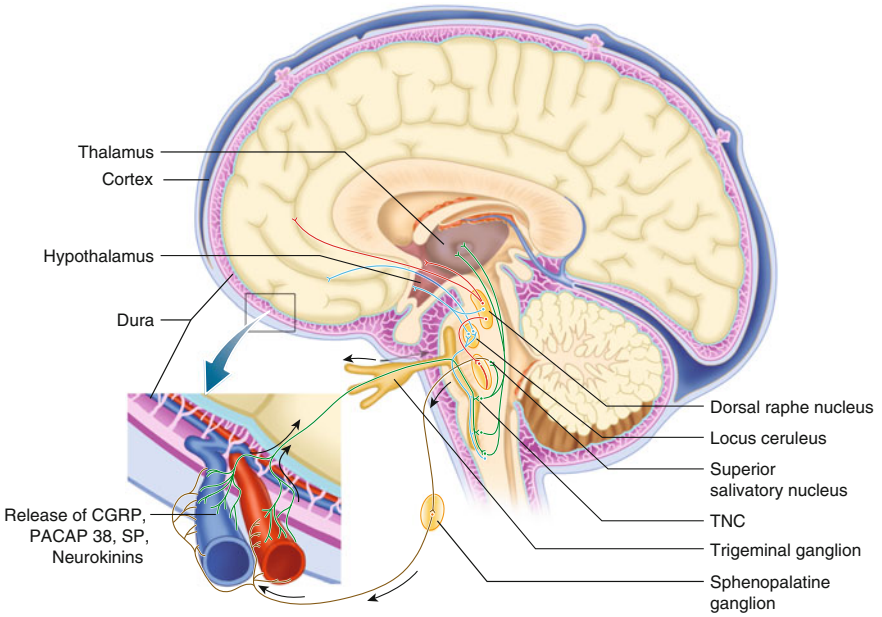

Fig. 2.1 The neuroanatomy of migraine (see text for details)

complex (TCC) by Goadsby and colleagues [3, 4]. The route from meninges to the TNC is the first-order afferent, and its firing is referred to as peripheral sensitization. Throbbing pain may be the clinical manifestation of peripheral sensitization [5].

In migraine activation, there is also stimulation of a brainstem-parasympathetic reflex, variously called the trigemino-parasympathetic reflex or the trigeminal autonomic reflex, in which parasympathetic efferents with cell bodies in the SSN synapse in the SPG. The exit via the SPG allows for targeting of this ganglion for acute and preventive treatment of migraine via blocks, ablation, or neuromodulation [6].

From the SPG, post-ganglionic parasympathetics travel to both the meninges and sinus-related organs, such as sinuses, eyes, and nose. These are second-order neurons [7]. Activation of this reflex, which involves VIP, results in sinus-like symptoms or cranial autonomic symptoms and signs in migraine. Nociceptive afferents return signals to the brain via the first division of the trigeminal nerve or ophthalmic nerve.

Once the pain mechanisms are engaged peripherally, the central anatomy is in turn sequenced. Pain signals ascend through upper brainstem to thalamus and on to cortex from the TCC. This allows for cortical reception of pain, activation of adjacent brainstem autonomic nuclei, parasympathetic stimulation resulting in sinus-like symptoms and signs, and, probably, a return to the meninges for further neuronal excitation and prolongation of the processes.

In addition, at some point the second-order neurons can start to fire without further peripheral input. This autonomous firing is referred to as central sensitization.

The clinical manifestation of central sensitization may be allodynia. Allodynia is the perception of non-painful stimuli as painful. Thus, at least part of the progression of migraine to central sensitization includes the patient finding touch painful (cutaneous allodynia), and photophonophobia may also be a form of allodynia [7].

Both CGRP and PACAP-38 levels rise during migraine attacks, and at least CGRP falls with treatment. CGRP and PACAP-38 both precipitate migraine attacks when administered intravenously [8–10].

There are CGRP and PACAP receptors centrally as well as peripherally, including on cranial parasympathetic ganglion and on the SPG, and these have been shown in both human and mammalian studies [10–14]. Edvinsson, commenting on this stated, "This provides evidence for an interaction between the parasympathetic and sensory systems" [1]. That is, these peptides have action peripherally and centrally, on the pain mechanisms and the processing, and specifically on the parasympathetic manifestations of migraine that clinically present as "sinus symptoms," ictal ocular and nasal signs and complaints.

The meningeal location of CGRP and some of its receptors raised the question of whether antagonism to its function would be sufficient to terminate migraine attacks or whether central anti-CGRP activity would be necessary for clinical effect. At least seven CGRP receptor antagonists, often referred to as small molecules or gepants, have all been effective in the acute treatment of episodic migraine [15–20]. At the time of this writing (December 2016), one gepant, ubrogepant, taken as-needed, is in Phase 3 trials for acute treatment of migraine and another gepant, atogepant, taken daily, is in a Phase 2 trial for migraine prevention.

Triptans and ergots suppress release of CGRP via a 5-HT 1D mechanism. 5-HT 1D receptor agonism also interferes with transduction of pain signals from the periphery to the brainstem. Triptan and ergot agonism at 5-HT 1B receptors results in vasoconstriction, a reversal of CGRP-induced vasodilation.

Four mABs prevented migraine in Phase 2 trials. Three of them are antibodies against the CGRP peptide ligand itself [21–23]; one is against the CGRP receptor [24]. Three of four of the mABs have effectively prevented both episodic and chronic migraine. Yet, they are large molecules and do not cross the blood–brain barrier [25, 26]. This means that termination of migraine acutely and prevention of migraine chronically can occur peripherally, at the CGRP receptor in the meninges.

Aura and Migraine

Most auras are defined by the International Classification of Headache Disorders, 3rd Edition, Beta version, as reversible neurologic events, lasting 5–60 min, followed by or accompanied by migraine or non-migrainous headache [27]. The

pathophysiology of migraine aura is an excitation of brain that is variously referred to as CSD or cortical spreading depolarization or cortical spreading depression.

CSD occurs with activation of the NMDA glutamate receptors. These receptors gate brain stimulation.

Most commonly, aura is visual and occurs with activation of the occipital cortex. The sequential excitation of the visual dominance columns of Hubel and Wiesel, which mediate edges, curves, movements, and other pre-formed visual percepts, account for the aura often being perceived as positive visual phenomena, although loss of vision, a negative visual phenomenon can also occur [28, 29].

Aura can occur elsewhere in the brain, and sensory and speech and language disturbances are next most common as typical auras. Auras can likely occur in brainstem and cerebellum as well.

In the wake of the depolarization, a wave of post-ictal depression of function occurs, and since this was first to be noted in physiology studies, the term CSD was coined, even though the primary event is excitation [30, 31]. Increased blood flow occurs with the depolarization, decreases with the post-ictal depression, and that decreased blood flow was mistakenly thought to be ischemia, while it is usually a 40% oligemia [32].

The familial hemiplegic migraines (FHM Types 1–3) all result in excess glutamate in the synapse. This excess glutamate is then available to stimulate NDMA receptors, and may account for the severity and duration of these more severe and prolonged auras.

The relationship of aura to migraine pain is not clear. Some migraineurs without clinical aura have CSD on functional imaging [33]. The clinical and pathophysiological questions are linked: does termination of CSD work in stopping migraine with and without aura, or just with aura?

Neuromodulation devices, such as single pulse transcranial magnetic stimulators and noninvasive vagal nerve stimulators, which both terminate CSD, sometimes appear to terminate or prevent migraine with and without aura, but these devices have other actions. A drug, tonabersat, aimed at inhibiting gap junctions or connexins necessary for propagation in CSD did not work to prevent both migraine with and without aura, although it did prevent migraine with aura alone [34]. Topiramate, valproate, propranolol, and amitriptyline significantly reduced CSD propagation speed, and methysergide (a long-acting ergot) showed a strong trend in doing so, but once again, do these medications work by this mechanism primarily, or secondarily [35]? Finally, magnesium and NMDA antagonists show some efficacy in acute and preventive treatment of migraine, but perhaps more so with aura [36, 37].

Burstein and colleagues [5] documented neurons connecting scalp, cortex, and meninges. In essence, they speculate a direct connection between cortical events such as aura and meningeal pain processes. This would account for both effects of anti-CGRP drugs on migraine and aura, and a possible conduit for botulinum toxin to suppress migraine mechanisms and aura.

In addition, activation of CGRP receptors leads to cytosolic calcium-dependent phosphorylation of glutamatergic NMDA-dependent neuronal activation. Thus, CGRP receptor activation indirectly leads to CSD [38, 39].

Zhang, Burstein, and colleagues found in rats that onabotulinumtoxinA inhibits C-type meningeal nociceptors via TRPV1 and TRPA1 activation. Activation of these receptors mediates release of SP and CGRP and modulates peripheral sensitization of nociceptors. There may be a link between the peripheral effects of botulinum toxin and anti-CGRP drugs and the central suppression of migraine and aura through physical and neurotransmitter processes [40, 41].

Genesis of Migraine

It is possible that the initial generation of migraine is central. Two functional MRI (fMRI) studies suggest a central generator in the area of the brainstem containing the dorsal raphe, locus ceruleus, and periaqueductal grey. One posited a central generator in the contralateral dorsal pons, [42] one in the same area in the ipsilateral [43]. The older study, done with Positron Emission Tomography (PET) was not as accurate in localization as the second study done with functional MRI, so the ipsilateral dorsal pons may the correct side.

There is continued controversy as to whether this area is where the migraine starts, or whether it is a central pain modulator. The argument over whether initiation of migraine is central or peripheral has been joined for decades [44].

The Burstein group suggests that migraine could begin peripherally, in the scalp or meninges, and communicate centrally to the cortex. The dramatic effectiveness of the anti-CGRP mAB biologics in migraine prevention, their effectiveness in both episodic and chronic migraine, even refractory chronic migraine with medication overuse headache, and the speed with which they work support this concept [45].

Conclusions

The initiation of migraine may be a central or peripheral process. In favor of a peripheral process are the discovery of neuronal pathways from scalp to dura and meninges to cortex, the inhibition in rats of cortical activation by botulinum toxin via TRPV1 and TRPA1 receptors, and the profoundly effective migraine prevention seen rapidly with anti-CGRP mABs which do not cross the blood–brain barrier and therefore have only initial peripheral effects. In favor of a central process are the activation of central neuromodulatory pathways and nuclei, specifically in the dorsal pons.

The genesis of aura is activation of NMDA glutamate receptors and CSD. CSD is a misnomer in that the activation associated with aura can be non-cortical and is an active depolarization. The ability to suppress CSD is associated with acute and preventive effects by drugs and neuromodulation devices, but whether this suppression alone is sufficient for either clinical effect is unresolved.

Migraine pain is due to both meningeal vasodilation and neurogenic inflammation. Presynaptic release of CGRP, VIP, SP, neurokinin A, and likely, PACAP-38 results in these processes. Triptans and ergots prevent release of CGRP, reverse CGRP-induced vasodilation, and interfere with return of the pain signal from periphery to brainstem. Anti-CGRP drugs and biologics can terminate migraine acutely (gepants) or prevent migraine (mABs).

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Chapter 3
Differential Diagnosis and Workup of the Headache Patient: Should I Order a Scan?

MaryAnn Mays

Introduction

Headache is a common symptom. Most individuals will experience some type of headache during their life time but it is only those that present abruptly and severely or those that are recurrent and disabling that bring the patient to the attention of the medical specialist. Although patients with headache will most often seek treatment by their primary care physician, the symptom of headache is seen as a chief complaint across all specialties, especially neurology, otolaryngology, and pain management specialists. In any given year about 50% of the general population has an active headache disorder, and more than 90% report a lifetime history of headache [1, 2].

Headaches that are causally linked to another disorder are classified as secondary headaches. Patients in whom the investigation excludes another disorder are then considered to have a primary headache disorder. The *International Classification of Headache Disorders,* third edition, beta version (ICHD-3) was published in 2013 and is a valuable resource for clinicians to utilize the validated criteria in diagnosing headache patients [3]. When a patient meets all but one criterion for the diagnosis, the headache diagnosis is labeled as "probable." It is important give a pause when there are atypical features or the patient does not fulfill the ICHD-3 criteria for a particular primary headache disorder, and once again consider the possibility of a secondary cause for the headache. The major primary and secondary headaches, including cranial neuralgias as classified by ICHD-3 are listed in Table 3.1.

This chapter will discuss how to recognize the three most common primary headache disorders, migraine, tension-type, and cluster headache utilizing the established ICHD-3 criteria. Frequently encountered secondary headaches will be highlighted, both those that present urgently as well as those nonlife-threatening

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Table 3.1 Classification of primary and secondary headaches and cranial neuralgias (ICHD-3)

Primary headaches	Secondary headaches and cranial neuralgias
• Migraine • Tension-type headache • Trigeminal Autonomic Cephalgias (TACs) – Cluster headache – Paroxysmal hemicranias – Short-lasting unilateral neuralgiform headache attacks (SUNHA includes SUNCT and SUNA[a]) – Hemicrania continua • Other primary headache disorders – Primary cough headache – Primary exercise headache – Primary headache associated with sexual activity – Primary thunderclap headache – Cold-stimulus headache – External-pressure headache – Primary stabbing headache – Nummular headache – Hypnic headache – New daily persistent headache (NDPH)	• Headache attributed to trauma or injury to the head and/or neck • Headache attributed to cranial or cervical vascular disorder • Headache attributed to non-vascular intracranial disorder • Headache attributed to a substance or its withdrawal • Headache attributed to infection • Headache attributed to disorder of homoeostasis • Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structure • Headache attributed to psychiatric disorder • Other headache disorders

[a]*SUNCT* Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, *SUNA* Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms

secondary headaches which are nonetheless equally concerning to the patient. It is important to understand the strategies to distinguish them from the primary headaches in order to know which patients require further diagnostic evaluation.

Primary Headache

The three primary headache disorders most commonly encountered are migraine, tension-type headache (TTH), and cluster headache. Patients with primary headaches experience recurrent headaches that are very stereotypical in nature. Both migraine and cluster have distinguishing features that allow them to be easily recognized by the clinician whereas tension-type headaches tend to be featureless. The headache most often experienced by the general population is tension-type headache. Although the patient experiencing migraine is more likely to seek medical advice for treatment due the more disabling nature of migraine. A study found that when patients present to their primary care office with a stable pattern of episodic but debilitating headaches, the likelihood that the patient had migraine or probable migraine was 94% [4]. Many patients never receive the correct diagnosis of migraine due to the fact that neck pain and autonomic symptoms are commonly

experienced by the migraineur and the clinician inappropriately attributes the symptoms to tension-type or sinus headache.

Migraine

Migraine affects 12% of the US population with greater prevalence in females (18%) compared to males (6%) [5]. Migraine, although an episodic disorder, is one of the most disabling conditions according to Global Burden of Disease Study. Migraine was found to be the sixth highest cause worldwide of years lost due to disability. The general category of headache disorders collectively was third highest [6]. Due to the disabling nature, migraineurs are more likely to seek medical attention through their primary care, emergency departments, and are more likely to miss work compared with their peers. With 30 million people in the US suffering from migraine alone, the socioeconomic burden is great, estimated to be $17 billion annually [7].

Migraine has distinct features which based upon can be classified into the two major subtypes of migraine without aura and migraine with aura (Tables 3.2 and 3.3). Individuals with migraine will describe a unilateral headache that is throbbing in nature and moderate to severe in intensity. The patient tends to avoid activities and prefers to lie down in a quiet dark room because of associated photophobia and phonophobia. Anorexia or nausea is common but vomiting is not. Additional history that may point to the diagnosis of migraine include a family history migraine, menstrual association, and triggering factors such as stress, weather, particular foods, and red wine.

Some migraines are associated with an aura. An aura is a neurological symptom experienced prior to or at the onset of a migraine headache which typically lasts 5–60 min. Auras are only experienced by 20% of migraineurs and most do not experience an aura with every headache attack. Occasionally, auras are not followed by a headache or are associated with a non-migraine type headache. The most

Table 3.2 Migraine without aura, ICHD-3 criteria

1. Patient must meet the following criteria for at least five attacks
2. Headache duration: 4–72 h (untreated)
3. Headache must meet any two of the following four features a. Intensity: moderate to severe b. Location: unilateral c. Quality: pulsating or throbbing d. Worsened by physical activity/activity avoidance
4. During the headache need to have at least one of the following a. Photophobia and phonophobia b. Nausea and/or vomiting
5. Secondary headaches have been excluded

Table 3.3 Migraine with typical aura, ICHD-3 criteria

1. Patient must meet the following criteria for at least two attacks
2. Aura consisting of one of the following symptoms which is fully reversible: visual, sensory, and/or speech/language, but no motor, brainstem, or retinal symptoms
3. Headache must meet at least two of the following four features: a. At least one aura symptom develops gradually over 5 min, and/or different aura symptoms occur successively b. Aura symptom lasts 5–60 min (Duration up to 180 min if auras occur in succession) c. 1 or more aura symptom is unilateral (aphasia is considered a unilateral symptom) d. Headache begins during or within 60 min of the aura onset
4. Secondary headaches have been excluded

common and typical auras are visual, sensory, and those associated with language dysfunction. Patients may also experience atypical auras consisting of brainstem, motor, or monocular visual disturbances but those are classified separately as migraine with brainstem aura, hemiplegic migraine, and retinal migraine, respectively. Aura should be distinguished from premonitory symptoms which typically occur hours to days prior to the onset of headache and include such symptoms as fatigue, hyperactivity, cravings, yawning, mood changes, and neck pain. After resolution of the headache, patients may be equally as disabled by the postdrome symptoms of fatigue, impaired concentration, dizziness, and overall feeling of weakness.

Patients who transform from an episodic pattern to a chronic pattern, with headaches occurring 15 days or more a month, are referred to as having chronic migraine. Patients with chronic migraine typically have near daily headaches which vary in intensity from mild to severe. The headache may be tension-type like on many days but by ICHD-3 criteria, the headache must fulfill the criteria for migraine on at least 8 days of the month and be responsive to migraine specific abortive therapies, such as triptans or ergots. Medication overuse has been linked to the development of chronic migraine. Chronic migraine should be distinguished from other chronic daily headaches including chronic tension-type headache, hemicrania continua (HC), and new daily persistent headache (NDPH).

Tension-Type Headache

Recurrent TTH is the second most common chronic condition affecting 1.6 billion people worldwide [6]. Despite being the most prevalent primary headache disorder, patients with episodic tension-type headaches rarely seek consultation from a physician unless the headache pattern becomes chronic in nature. More commonly it is that the episodic migraineur that will be misdiagnosed as having TTH due to the high frequency of associated neck pain and the fact that migraine is commonly triggered by stress. TTH is classified by ICHD-3 based upon the frequency of

Table 3.4 Tension-type headache, ICHD3 criteria

1. Headache lasts from 30 min to 7 days (may be unremitting in chronic TTH)
2. Headache must have at least two of the following four features a. Intensity: mild to moderate, not severe b. Location: bilateral c. Quality: pressure, non-throbbing d. Not aggravated by physical activity
3. During the headache must have both of the following symptoms a. No nausea or vomiting b. No more than one of photophobia or phonophobia
4. Secondary headaches have been excluded

occurrence (infrequent, frequent, and chronic) as well association with and without pericranial tenderness. Infrequent episodic TTH occur on <1 day a month on average whereas frequent episodic TTH occur on ≥ 1 but <15 days per month for at least 3 months. TTH that occur >15 days per month for at least 3 months are classified as chronic TTH. Investigation to exclude secondary causes of headache is necessary in all patients experiencing daily headache. Chronic TTH have greater associated disability than episodic TTH and consequently a greater negative impact on quality of life. Individuals with frequent or chronic TTH benefit from medical management of their headaches as well as education on avoiding medication overuse.

Clinicians are often challenged in distinguishing tension-type headaches from milder migraines and in these patients the clinician should take into consideration a prior history of motion sickness, prior personal or family history of migraine, possible migraine triggers, and the presence of nausea. These factors may tip the clinician off in considering the diagnosis of mild migraine and treating the patient with a migraine-specific abortive such as a triptan. If the patient has pure episodic tension-type headache, they will not respond to a triptan but a migraineur with tension-type like headache will get relief of symptoms. Table 3.4 lists the ICHD-3 criteria for TTH.

Cluster Headache

Cluster headache (CH) is a primary headache disorder grouped under the classification of the trigeminal autonomic cephalgias (TACs). Other headaches grouped into the TACs subgroup include paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks (SUNHA) which encompasses those with conjunctival injection and tearing (SUNCT) and those with cranial autonomic symptoms (SUNA), and HC. These headaches are notable for their unilaterality as well as prominent associated autonomic symptoms due to parasympathetic activation and sympathetic paresis. Cranial autonomic features include lacrimation,

Table 3.5 Distiguishing features of the trigeminal autonomic cepahalgias

Features	Cluster	Paroxysmal hemicrania	SUNHA	Hemicrania continua
Gender preference (F:M)	Male (1:4)	Episodic: none Chronic: female	Male (1:2)	Female (2:1)
Pain severity	Very severe	Very severe	Severe	Mild to moderate with severe exacerbations
Attacks/day	1–8	1–40	1–100	Continuous
Attack duration	15–180 min	2–30 min	1–600 s	Peaks last hours to days
Circadian periodicity	Present	Absent	Absent	Absent
Triggers	Alcohol	Mechanical/neck movement	Cutaneous stimuli Neck movement	Alcohol, stress
Family history	Yes	No	No	Yes
Indomethacin responsive	Occasional	Yes	No	Yes

SUNHA Short-lasting unilateral neuralgiform headache attacks

conjunctival injection, nasal congestion, rhinorrhea, ptosis, and eyelid edema occurring ipsilateral to the side of pain. The TACS are distinguished based upon the headache frequency, duration, severity, pattern of occurrence and responsiveness to particular treatments, as listed in Table 3.5.

CH is the most common of the TACS, although least common of the primary headache disorders with a lifetime prevalence of 0.12% [8]. CH is more common in males. The pain of CH is very severe and sharp in nature involving the periorbital and temporal region accompanied by unilateral autonomic symptoms. The pain remains side-locked during attacks but may occasionally shift sides in subsequent bouts. CH occurs in cycles with a pattern of daily headache attacks for weeks to months followed by a remission that last months to years. The attacks have both a circadian and circannual periodicity. CH has been noted to occur with alarm clock periodicity at the exact same time each day as well as predictable and seasonal recurrences during the changing of the clocks for daylight savings time. Attacks may be triggered by alcohol and REM sleep and are quickly aborted by subcutaneous sumatriptan and inhaled oxygen. Diagnostic criteria for cluster headaches are listed in Table 3.6. The majority of CH is episodic but some patients develop chronic CH for which there is no remission from attacks. Differential diagnosis for the TACs includes migraine, hypnic headache, trigeminal neuralgia, idiopathic stabbing headache, and rhinogenic headache. Pituitary and other structural lesions of the brain have been known to mimic the TACs so it is important to obtain neuroimaging on all patients to exclude secondary causes [9, 10].

Table 3.6 Diagnostic criteria for cluster headaches, ICHD-3

Cluster headache
A. Patient must meet the following criteria for at least five attacks
B. Severe or very severe unilateral orbital, supraorbital or temporal head pain lasting 15–180 min (untreated)
C. Headache either or both of the following features 1. ≥ 1 of the following symptoms or signs, ipsilateral to the headache a Conjunctival injection or lacrimation b Nasal congestion or rhinorrhoea c Eyelid edema d Forehead and facial sweating e Forehead and facial flushing f Sensation of fullness in the ear g Miosis and/or ptosis (Horner's syndrome) 2. A sense of agitation or restlessness
D. Attacks have a frequency between qod up to 8/day, for >50% of active cycle
E. Secondary headaches have been excluded
Episodic cluster headache
• At least 2 cluster attacks lasting a period of 7 days up to 1 year, followed by pain-free periods lasting at least 1 month
Chronic cluster headache
• Cluster attacks occurring for a year or more without a remission period, or with remissions lasting <1 month

Secondary Headache

Headache may be a symptom of another disease and when there is evidence of a causal relationship, the headache is defined as a secondary headache. Secondary headaches may mimic the pattern of a primary headache or co-exist in a patient with a known primary headache disorder. The vast majority of patients that present to the emergency department or primary care office with headache will have a primary headache disorder. Less than 5% will have headache as a symptom of underlying pathology which may pose immediate threats to the life and welfare of patients [11]. The task of identifying such headaches is relatively easy in the acute setting but more problematic for those that present with chronic head pain. Secondary headaches are classified based up the underlying cause. Numerous conditions may be the cause of headache and are grouped into eight subgroups by the ICHD-3 as listed in Table 3.1.

The challenge to clinicians is that secondary headaches lack any defining headache characteristics and may mimic or co-exist with a primary headache disorders. Typically, the secondary headache will improve or worsen in parallel with the improvement or worsening of the underlying causative disorder. With age comes the increased risk of secondary headaches. Secondary headaches are found in 15% of those over the age of 65 years yet in only 1–2% patients younger [12]. Pediatric patients are very unlikely to have an intracranial tumor as a cause of headache in the

Table 3.7 Established causes of secondary headache

• Posttraumatic	• Low cerebrospinal fluid pressure
• Ischemic stroke/TIA	• Brain tumors
• Intracranial hemorrhage (intracerebral, subarachnoid, subdural)	• Encephalitis/meningitis
• Cerebral venous thrombosis	• Chiari I malformation
• Vascular malformations (aneurysm, arteriovenous malformations)	• Acute hypertensive crisis
• Reversible cerebral vasoconstriction syndrome (RCVS)	• Homeostasis disorders
• Carotid or vertebral dissections	• Toxic substances
• Vasculitis (GCA, primary angiitis of the central nervous system)	• Medication induced/medication overuse
• Hydrocephalus	• Cervicogenic
• Pituitary apoplexy	• Temporomandibular disorder
• Idiopathic intracranial hypertension (IIH/pseudotumor cerebri)	• Sinusitis
	• Acute angel closure glaucoma
	• Trigeminal neuralgia and painful trigeminal neuropathies
	• Other cranial neuralgias

absence of neurological signs and symptoms. Red flags in children are similar to those in adults but also include age less than 6 years, occipital headache, and absence of a family history of migraine [13, 14]. Not all causes of secondary headache will be discussed in this chapter but Table 3.7 lists the most common causes as well as those less common, but still important to consider in the differential diagnosis of acute and chronic headache evaluation.

Headache Associated with Vascular Disease

Headache may be a presenting symptom or the sequela of vascular disease such as subarachnoid hemorrhage, intracranial hemorrhage, stroke, or vasculitis. Table 3.8 lists the most common vascular disorders which have been known to cause headache. A very severe headache that reaches maximal intensity within seconds to a minute is referred to as a thunderclap headache. Patients who present with "the worst headache of my life" or thunderclap headache require emergent evaluation. Abrupt and severe headache onset is the classic presentation of subarachnoid hemorrhage (SAH) due to cerebral aneurysm rupture [15]. However, this diagnosis is missed in up to 25–50% of patients. A sentinel headache may occur in 50% of unruptured cerebral aneurysm in the days to weeks prior to SAH. The risk of spontaneous rupture occurs when aneurysms reach 7 mm in size. The mean incidence of rupture occurs at the age of 50 years. In patients with recurrent thunderclap headache over a few days to weeks, consider the diagnosis of reversible vasoconstriction syndrome (RCVS) which is diagnosed by the presence of diffuse segmental cerebral arterial vasoconstriction on cerebral angiogram. Certain clues in the history may point to other common causes of thunderclap headache (Table 3.9) [16].

Table 3.8 Vascular disease associated with headache

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

Table 3.9 Clues to the diagnosis of thunderclap headache

Common causes	Clues
Subarachnoid hemorrhage	Meningismus, loss of consciousness, seizure, EKG abnormalities
Reversible cerebral vasoconstriction syndrome	Exertion, post-partum, migraine, illicit drugs, prescription medications: antidepressants, stimulants, nasal decongestants, triptans
Cerebral infection	Fever, meningismus
Cerebral venous sinus thrombosis	Post-partum, dehydration, hypercoagulability, papilledema, seizure, worse with Valsalva
Cervical artery dissection	Trauma, chiropractic treatment, Horner's syndrome, neck pain
Complicated sinusitis	Fever, ears, nose and throat symptoms, worse supine
Hypertensive crisis/posterior reversible encephalopathy syndrome (PRES)	Elevated BP (>180/120 mmHg), papilledema, posterior headache, visual changes
Intracerebral hemorrhage	Focal signs, seizure, hypertension, anticoagulation
Ischemic stroke	Focal signs, seizure, atrial fibrillation
Spontaneous intracranial hypotension	Recent LP, trauma, worse upright position, pulsatile tinnitus, muffled hearing, dizziness
Subdural hematoma	Recent fall, memory loss, gait difficulties

It is important to recognize other headache presentations that occur as a result of vascular disease. Some headaches may present acutely over hours or days, just prior to or coinciding with the onset of neurological deficits as more commonly seen with stroke, TIA, intracranial hemorrhage, cerebral venous thrombosis, and cervical artery dissection. Headaches are usually ipsilateral to the side of the vascular event.

More indolent headache presentations may be seen with giant cell arteritis (GCA) or primary angiitis of the central nervous system (PACNS). GCA occurs exclusively in individuals over the age of 50 years and more commonly in women. The headache is most often temporal in location with associated temporal artery tenderness and decrease in arterial pulse. Associated symptoms often include scalp tenderness, jaw claudication, and visual loss. Patients may have additional symptoms of polymyalgia rheumatic. Prompt diagnosis and treatment with corticosteroids is required to prevent the complication of permanent visual loss. Elevated sedimentation rate (>50 mm/h) and temporal artery biopsy are confirmatory of the diagnosis. A rarer form of vasculitis is PACNS. This form of vasculitis also occurs most often over the age of 50 years but is more common in males. Cognitive changes, focal neurological deficits, and evidence of strokes on neuroimaging are suggestive of the diagnosis. Inflammatory markers are not likely to be elevated but CSF analysis often reveals a mild pleocytosis and elevated protein. Cerebral angiography may reveal the characteristic beading pattern suggestive of segmental arterial stenosis but often leptomeningeal and brain biopsy are necessary to confirm the diagnosis.

Headache Due to Intracranial Hypertension and Hypotension

Headache may occur as a response to changes in cerebrospinal pressure, either elevated or decreased. Idiopathic intracranial hypertension (IIH) was previously referred to as pseudotumor cerebri. This diagnosis should be considered in patients with daily, moderate intensity, pressure-like headaches. This headache may worsen with exertion and patients often complain of visual obscurations, pulsatile tinnitus, diplopia, and neck pain. Papilledema is most often present on examination but the absence of does not exclude the diagnosis. CSF opening pressure of greater than 250 mm H_2O in adults and 280 mm H_2O in children is considered diagnostic. Improvement of headache following the removal of CSF is one of the ICHD-3 criteria for IIH.

In contrast, patients may develop a headache caused by low CSF pressure (<60 mmHg) which may be the result of a CSF leak that has occurred either following a prior lumbar puncture (LP) which has caused a persistent dural tear or a leak that has occurred spontaneously. The classic history of a low CSF pressure headache is a positional headache that worsens in the upright position but improves upon lying down. MRI of the brain with gadolinium may demonstrate findings supportive of the diagnosis of low CSF pressure including pachymeningeal

enhancement, venous engorgement, cerebellar tonsillar descent, and subdural fluid collections [17].

Medication Overuse Headache

Medication overuse headache (MOH) is the most common cause of a secondary headache. This headache tends to have both migraine and tension-type features and is unresponsive to abortive and preventative medications. Patients report additional symptoms of mood changes, sleep disturbances, autonomic symptoms, vasomotor instability, and neck pain [18]. When there is a change in the pattern of a primary headache disorder from an episodic headache transforming into a chronic daily headache ($\geq$ 15 days a month), the patient should be questioned specifically about the frequency of use of analgesics of any type to abort headache pain. Use acute abortive headache medications more than 10 days a month for more than 3 months puts the patient at risk. MOH may occur in the setting of very limited use of butalbital (>5 days/month) or opioids (>8 days/month) and thus it is best to avoid prescribing these medications as abortive agents for headache pain [19]. Patients should be advised that abstaining from or at a minimum limiting the use of analgesics to 2 days or less a week, is likely to revert the patient back from a chronic to an episodic pattern. The success rate of treatment after withdrawal of the offending agent and initiation of prophylactic therapy is around 50–70% but it may take 2–3 months for the benefit to be noted [20].

Sinus Headache

Patients often present with self-diagnosed sinus headache because of the frontal and maxillary location of head pain, associated autonomic symptoms such as rhinorrhea, nasal congestion, and lacrimation. Patients may relate occurrence of head pain due to weather and seasonal changes [21, 22]. More often than not, sinus headaches are likely migraine [23]. Sinusitis is an uncommon cause of recurrent headache. Although it now accepted that chronic sinus disease may be the source of persistent headache. The improvement of headache with antibiotic treatment should not be used as proof of causality that the headache is due to sinus disease. Rhinogenic headaches are a more appropriate term to refer to headaches or facial pain that is secondary to underlying nasal or sinus pathology [24].

Both migraine and chronic rhinosinusitis are common diseases, each occurring in about 12% of the United States population [5, 25]. Chronic rhinosinusitis, allergic rhinitis, and migraine have been found to be comorbid conditions [24, 26]. Oral, nasal, and sinus pathology have been known to trigger a migraine so differentiating the cause of headache can be challenging. Tables 3.10 and 3.11 outline the features of headache due to acute and chronic rhinosinusitis per the ICHD-3

Table 3.10 Headache attributed to acute rhinosinusitis, ICHD-3 criteria

A. Headache must meet any 2 of the following 4 features as evidence of causation
1. Occurrence of headache and rhinosinusitis are temporally related 2. One or both of the following features: a. Headache and rhinosinusitis worsen in parallel b. Headache and rhinosinusitis improved or resolved in parallel 3. Applied pressure over paranasal sinuses worsens the headache 4. Headache is located on the same side of the sinusitis, if unilateral
B. Evidence of acute rhinosinusitis as documented by clinical, nasal endoscopy or neuroimaging
C. Secondary headaches have been excluded

Table 3.11 Headache attributed to chronic or recurring rhinosinusitis, ICHD-3 criteria

A. Headache caused by chronic infectious or inflammatory paranasal sinus disease must meet any 2 of the following 4 features as evidence of causation: 1. Occurrence of headache and chronic rhinosinusitis are temporally related 2. Headache severity waxes and wanes in parallel with symptoms of chronic rhinosinusitis such as sinus congestion, nasal obstruction and postnasal drip 3. Applied pressure over paranasal sinuses worsens the headache 4. Headache is located on the same side of the sinusitis, if unilateral
B. Evidence of current or past infection or inflammation of paranasal sinuses as documented by clinical, nasal endoscopy or neuroimaging
C. Secondary headaches have been excluded

classification. Clinicians must also consider if headache is due to other disorders of the nasal mucosa, turbinates, or septum in which case may improve after local anesthesia in the region of the suspected lesion. This was previously termed mucosal contact point headache. Rhinogenic headache should be differentiated from headache caused by temporomandibular joint dysfunction (TMD), which is associated with jaw movements that are restricted and produce pain, crepitus, and popping upon opening along with point tenderness at the joint.

Evaluation

Headache evaluation and management relies heavily on the clinician's ability to take a thorough history. Diagnosis often relies on pattern recognition as well as eliciting red flags. The mnemonic "SNOOP" (Table 3.12) which was developed by Dr. David Dodick is helpful in providing a systematic approach to recalling those clinical clues helpful identify secondary headaches [27, 28]. Other important information to obtain includes if there is a positional nature to the headache, current medications (such as nitroglycerin and anticoagulants), and use of illicit substances. Complete physical and neurological examination is essential with particular attention to vital signs, presence or absence of meningismus, eye exam including

Table 3.12 Red Flag mnemonic "SNOOP" (adapted from Dodick)

Systemic signs/symptoms (fever, weight loss, myalgias, meningismus)
Systemic disease (HIV, cancer, autoimmune disease)
Neurologic symptoms or abnormal signs (altered of consciousness, focal neurological deficits)
Onset: first and worst, sudden or abrupt (thunderclap), with exertion/Valsalva
Older age of onset: After the age of 50 (giant cell arteritis, malignancy)
Pattern change: first or different headache type, progressive, unremitting, postural worsening
Previous headache history: attack frequency, severity or clinical features

funduscopy, and a head and neck evaluation to look for evidence of sinus disease, TMJ or cervical spine disease. When red flags are raised or neurological deficits are identified additional investigation with laboratory testing or neuroimaging will most often identify the cause of head pain [29]. Also helpful in obtaining the history is eliciting "green flags" or comfort signs that are more suggestive of a primary headache disorder. These comfort signs consist of the patient presenting with a long history of an established headache pattern for greater than 6 months, changing location of headache, family history of similar headaches, specific triggers such as alcohol, foods, odors, weather, and menstrual cycle as well as a normal neurological exam [30].

Neuroimaging

In patients presenting to the emergency department with new onset acute severe headache, neuroimaging is always warranted. In patients with chronic history of recurring episodic migraine or TTH in which there is an established pattern of occurrence, neuroimaging is of low diagnostic yield, 0.5% [31]. Imaging is more likely to identify an incidental finding that has no bearing on the headache presentation and may be of no clinical concern but may lead to additional testing, cost, discomfort, and anxiety for the patient. The clinician should not be misguided into thinking that when their clinical diagnosis is uncertain, that neuroimaging will provide a diagnosis or assist in the therapeutic decision-making. However, there is value to the clinician in obtaining imaging in patients who are present with a changing headache pattern or red flags in their history, are unresponsive to therapy, or exhibit focal neurological findings on examination. The American College of Radiology (ACR) has developed the ACR Appropriateness Criteria® (AC) to assist physicians and determining the most appropriate imaging to select for specific clinical conditions and patient population based upon evidence-based guidelines [32]. This is a valuable reference which clinicians should consult prior to ordering

tests for evaluating headache. In addition to the ACR, the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) have also have published guidelines and also advise against the routine use of imaging in migraine patients with normal neurological examinations [33, 34].

The American Headache Society partnered with the American Board of Internal Medicine (ABIM) Foundation's in their initiative *Choosing Wisely* to provide recommendations in avoiding medical care that is of low-value and potentially harmful. In regards to neuroimaging, they recommended: (1) Patients that meet criteria for migraine and have a stable pattern of headache, do not require neuroimaging and (2) For patients in whom diagnostic imaging is indicated, magnetic resonance imaging (MRI) is preferred over computer tomography (CT), except in those cases that present acutely in the emergency department [35]. MRI is more sensitive than CT in detecting structural abnormalities of the brain and therefore is actually more cost-effective [36]. Avoiding the exposure and harmful effects of ionizing radiation associated with CT scans is particularly important in the headache patient who is a frequent flyer to the emergency department. Important to consider is that children are more sensitive to radiation than adults and are thus at greater risk for radiation-related cancer. One study found that one-third of these projected cancers were related to CTs performed at the ages of 35–54 years [37]. However, in those patients with contraindications to MRI, CT with contrast is a reasonable option.

Angiography is useful in diagnosing patients with an underlying vascular malformation, aneurysm, vasculitis, or dissection. Although conventional catheter angiography has long been the gold diagnostic standard, it does carry a low risk ($\sim$0.5%) of neurological complications and is not readily available at all institutions. Improvements in techniques and ease of obtaining CT angiography (CTA) and MR angiography (MRA) have made these test suitable diagnostic alternatives. MRA without contrast is most often utilized when imaging intracranial vessels. When there is specific concern for a cerebral aneurysm, CTA is preferred over MRA as it has a sensitivity and specificity comparable to conventional angiography although conventional angiography still has the best resolution for aneurysm <4 mm [38, 39]. Unruptured aneurysms with the greatest risk of rupture are larger than 7 mm in diameter. MRI with contrast can be useful for monitoring patients post clipping or stenting as the contrast minimizes the metallic distortions [32]. Gadolinium is to be avoided in patients with renal dysfunction who are receiving dialysis or have a low glomerular filtration rate (GFR < 30 mL/min/1.73 m^2) due to the risk of nephrogenic systemic fibrosis. It also should not be used in pregnant women. For diagnosis of craniocervical arterial dissections, a contrast enhanced MRA is generally preferred although has similar sensitivity and specificity to CTA [40]. MR or CT venography are recommended in those patients who are suspected to have cerebral venous thrombosis or who are suspected to have increased intracranial pressure as evidenced by the presence of papilledema.

Imaging is unnecessary in most cases of uncomplicated acute and subacute rhinosinusitis [41]. Conversely, in patients with unremitting headaches related to chronic or recurrent sinonasal disease, a sinus CT without contrast is appropriate to

guide decision-making. Sinus CT can be useful in assessing the paranasal sinuses and anatomic structures when used in conjunction with clinical examination including endoscopy. MRI of the brain with and without contrast may be necessary if there is concern for fungal infections, mass lesion, or ocular/intracranial involvement of the infection.

For evaluating patients with trigeminal neuralgia refractory to medical therapy, an MRI/MRA of the brain with and without contrast with 3D constructive interference in steady state imaging (CE-CISS) can help identify neurovascular contact as a cause of facial pain [42]. Temporal artery biopsy is the gold standard for patients suspected to have GCA however biopsies are positive only in a small percentage of patients, <20%. High-resolution MRI of the scalp arteries may be a useful initial screening tool with a reported high sensitivity (93.6%) and negative predictive value (98.2%) of diagnosing GCA [43]. Temporal artery ultrasound may be a useful adjunct to aid in the diagnosis if available, but a negative test does not exclude the diagnosis.

Laboratory Testing

In general, routine laboratory testing is not helpful in the diagnosis of headache. Many clinicians will obtain a baseline complete blood count (CBC), chemistry profile (CMP including liver and renal function tests), and thyroid studies/thyroid-stimulating hormone (TSH) prior to initiating medication treatments. In patients over the age of 50 years with new onset of headache, obtaining an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are essential in excluding the diagnosis of GCA. Antinuclear antibodies (ANA) and rheumatoid factor (RF) is helpful in evaluating for other autoimmune diseases that may be associated. Patients who present with headache and neuropsychiatric symptoms should have testing for anti-NMDA-receptor antibodies associated with autoimmune encephalitis. HIV and Lyme disease can also produce headache and encephalitis. In patients who have had a stroke, cerebral venous thrombosis, or evidence suggestive of vasculitis, testing for lupus anticoagulant and anticardiolipin antibodies as well as obtaining a hypercoagulable profile is recommended. A toxicology screen may also reveal illicit drug use that may be the etiology of a vasculitis or be suggestive of opioid abuse. Drug levels may help monitor compliance although therapeutic levels have not been established for headache. In colder months, clinicians should also always consider the possibility of carbon monoxide intoxication as a cause as this is easily checked by obtaining a carboxyhemoglobin level. Genetic testing is not part of the routine evaluation of headache disorders but may be warranted if considering the diagnosis of familial hemiplegic migraine, MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) or CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy).

Electroencephalography (EEG) is no longer recommended in the routine evaluation of headache patients to rule out a structural cause unless the patient is reporting additional symptoms that may be suggestive of a seizure or is encephalopathic. Ophthalmology consultation may be useful when visual complaints are not typical of aura, papilledema is present, there are complaints of diplopia or vision loss or there is concern for glaucoma. Contrary to popular belief, it is very uncommon for refractive errors to be the isolated cause of headache [44]. Nasal endoscopy is useful for evaluating for sinusitis.

Cerebrospinal Fluid Analysis

A LP to obtain cerebrospinal fluid (CSF) is an important clinical tool in investigating possible subarachnoid hemorrhage, meningitis/encephalitis, malignancy or causes of papilledema. In the patient that presents with a thunderclap headache, severe and sudden in onset, an LP is necessary to rule out the possibility of a SAH if the patient presents for evaluation greater than 6 h after presentation. Recent studies suggest that a LP may not be necessary if patient within 6 h after headache onset as the negative predictive value of head CT scan performed onset is 100% when performed within that time frame [45]. If the patient presents after 6 h or there is an atypical presentation, most clinicians will perform a LP in completing the evaluation for thunderclap headache. LP may be falsely negative when performed within the first 12 h or greater than 2 weeks after bleeding [46]. CSF spectrophotometry, when available, is able to detect xanthochromia in 100% of cases [47]. When headache presents acutely with fever and meningismus, an LP is necessary to rule out infection. In a normal individual, the CSF white blood count (WBCs) should be less than 5. In the case of a traumatic LP, one additional WBC is allowed for every 700 red blood cells (RBCs). Obtaining cell counts on tube 1 and 4 can also help to differentiate a traumatic tap from subarachnoid hemorrhage. CSF glucose level should be two-thirds of the serum glucose level. The presence of hypoglycorrhachia is suggestive of bacterial, fungal, or tuberculosis meningitis, sarcoidosis or carcinomatosis. CSF analysis is also of utility in diagnosing central nervous system vasculitis as the CSF protein is generally elevated. Opening pressure is helpful if diagnosing IIH or hypotension. Normal CSF pressure ranges from 70 to 250 mm of H_2O.

Conclusion

Headache is a presenting symptom of many different disorders. It is the clinician's responsibility to complete a thorough history and examination on every patient who presents in order to distinguish primary from secondary headaches. The inability to timely diagnose a secondary headache can have catastrophic consequences for the patient. Misdiagnosing the type of primary headache disorder can lead to ineffective

treatment options for the patient which only adds to their suffering and disability related to the headache pain and associated symptoms. Using the ICHD-3 criteria for headache disorders is a useful guide for the practitioner. Judicious use of diagnostic testing in view of each clinical presentation can add to patient care as well as maintain cost-effective medicine.

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Chapter 4
Pharmacological Management of Migraine

Benjamin Saunders and Brian E. McGeeney

Introduction

An effective migraine management plan can be a very difficult regimen to establish. Of the utmost importance is the establishment of a treatment partnership with the patient which will then facilitate the trust needed to establish a treatment plan and adherence to that plan. Failure to gain the trust of the patient or set appropriate goals quickly leads to noncompliance and disengagement. Experienced Headache Medicine practitioners hear this again and again. Over time, management plans can be optimized and tailored to individual needs and preferences as there is great individual variability. An optimized management plan encompasses not only education but behavioral treatments as well as pharmacological therapy. Educating patients on the nature and mechanism of their disorder will not only encourage dialogue with the treating physician but also empower patients to actively participate in their migraine headache management. The concept of an inherent sensitivity must be appreciated, avoiding an endless search for a 'cure.' Encouraging the patient to keep a headache diary for both diagnostic and as a guide to treatment purposes can provide the clinician with previously unrecognized patterns of headache, triggers, and a better tally of burden.

Behavioral modifications can greatly compliment pharmacological management. Strategies can encompass diet, exercise, proper sleep hygiene, hormonal fluctuations, noise, lights, fragrances/fumes, stress management and exercise, as well as other trigger avoidance. Often behavioral modification offers a slower treatment response but fosters patient engagement in their management. In particular, these strategies can be important when treating patients in which pharmacological

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management may be limited or unresponsive, for instance in pregnancy or with comorbid conditions.

This section will focus on the pharmacological management of migraine. Acute or abortive therapy refers to treatment offered to the patient during an attack, with the goal of limiting pain, disability, and limiting progression of the migraine. Prophylactic therapies are longer term daily medications taken to reduce the incidence, intensity, and duration of migraine. Preemptive treatments are offered when a known headache trigger exists, such as migraine related to the menstrual cycle or with intense physical activity. Patients with frequent headaches will most likely require a combination of therapies. In this chapter, we will introduce the different types of phamacological therapies, their uses, and discuss how they can fit together into a treatment plan.

Abortive Medications

These are medications that acutely treat a migraine attack (Table 4.1). The choice of treatment typically depends on attack intensity, speed of migraine onset/progression, and frequency of migraine, along with side effects and tolerability of medication options. Abortive medications can be divided into two categories-specific migraine treatments and nonspecific medications used to treat migraine. Further, outpatient treatments differ when compared to emergency department (ED) or inpatient care. Specific migraine therapies include ergotamine containing compounds and triptans. These are typically only used for the purpose of treating migraine. Please note that response, even complete response to triptans or ergotamine is not pathognomonic of migraine as plenty of undiagnosed secondary headaches have been so treated.

Nonspecific treatments are medications that are used for a wide variety of pain disorders and include nonsteroidal anti-inflammatory drugs (NSAIDs), other analgesics, neuroleptics, antiemetic agents, and steroids which also have a role in the management of migraine. When all fails, simply putting the patient to sleep solves the problem at least temporarily and avoids the need for urgent medical evaluation (including ED visits). Use of diphenhydramine, the sedative dopamine antagonist antiemetics (for instance promethazine) or benzodiazepines are used, among other options to facilitate sleep.

Serotonin Receptor Agonists (Triptans)

Medications used to treat migraine acutely should be able to work rapidly, with few side effects, be cost-effective, and get the patient as functional as possible in a shorter period as possible. The closest class of medications to an ideal migraine treatment is the triptans and they have been the drug of choice for patients who fail NSAID therapy [1, 2]. There are seven different triptans in the United States which

Table 4.1 Medications used in the treatment of acute migraine

• ASA – 650 to 100 mg q4–6 h • Acetaminophen[a] – 325–1000 mg q4–6 h	• NSAIDS – Ibuprofen (Advil, Motrin, Nurofen)[b] 200–400 mg q4–8 h Single doses up to 800 mg – Naproxen sodium (Aleve) 220 mg q4–6 – Ketoralac (toradol) 30 mg q6 – Diclofenac (Cataflam) 18–35 mg q8 h
• Triptans – Sumatriptan (Imitrex) – Eletriptan (Relpax) – Frovatriptan (Frova) – Almotriptan (Axert) – Naratriptan (Amerge) – Zolmitriptan (Zomig) – Rizatriptan (Maxalt)	• Barbituatess – Butalbitol, ASA and Caffeine (Fiorinal) 1–2 tabs q4-6h – Butalbitol, Acetaminophen and Caffeine (Fioricet) 1–2 tabs q4–6 h Use should be Limited to avoid rebound headaches, up to 4 tabs daily and not more than 2 days per week
• Ergot Alkaloids – Dhydroergotamine mesylate (DHE) 1 mg IV q8 h	• Phenothiazines – Prochlorperazine (Compazine) 5–10 mg PO q6–8 h – Chlorpromazine (Thorazine) 10–25 mg PO q4–6 h – Metoclopramide (Reglan) 10 mg IM/IV q6–8 h
• Opiates – Codeine 30 mg, APAP 300 mg (Tylenol #3) 1–4 tabs q4–6 – Oxycod one/APAP, 2.5/325, 5/325, 7.5/325, 10/325 (Percocet, Percodan) 2.5–10 mg Oxycodone q6 h – Oxycodone 5 mg, Ibuprofen 400 mg (Combunox) 1 tab qd–6 h Butorphanol Nasal Spray (Stadol) • 1 spray (1 mg), may repeat in one hour, max dose is 4 sprays per day Limit use as there is high potential for abuse in Migraine patients	• Other OTC medications – Acetaminophen 250 mg, ASA 250 mg, Caffeine 65 mg (Excedrin Migraine) – Take 2 tabs at onset of headache, do not exceed 2 tabs in 24 h – Ibuprofen (Advil Migraine) 200–800 mg q4–8 h

ASA Aspirin; *NSAID* Nonsteroidal anti-Inflammatory Drug; *OTC* Over The Counter; *APAP* acetaminophen

[a]Maximum recommended APAP dose is 4 g/day

[b]Maximum recommended Ibuprofen dose is 2400 mg/day

offer numerous dosage forms and delivery methods (Table 4.2). Common advice is to use triptans with NSAIDs for a better outcome and sumatriptan is even bundled with naproxen in one branded tablet option. A common mistake is to under-dose

Table 4.2 Triptans

Drug	Dosing/formulation	Comments
Sumatriptan (Imitrex)	• SQ 6 mg (auto injector); may repeat in 2 h, max dose 12 mg in 24 h • Intranasal 5–20 mg; 1 spray in nostril per dose, may repeat in 2 h, max dose 40 mg in 24 h • Oral 25–100 mg may repeat in 2 h, max 200 mg in 24 h	• Fast onset or action with SQ: 10–15 min • Oral onset of action: 30–90 min
Eletriptan (Relpax)	Oral 20–40 mg may repeat in 1–2 h, max dose 80 mg in 24 h	• Onset or action: 60–90 min
Frovatriptan (Frova)	Oral 2.5 mg, may repeat in 2 h, max dose 7.5 mg in 24 h	• Onset or action: 120–240 min • Longer duration or action
Almotriptan (Axert)	Oral 6.25–12.5 mg, may repeat in 2 h, max dose 25 mg in 24 h	• Onset or action: 30–120 min • 40% excreted unchanged by kidneys
Naratriptan (Amerge)	Oral 1–2.5 mg, may repeat in 4 h, max dose 5 mg in 24 h	• Onset or action: 60–180 min • Long duration or action • 50% excreted unchanged by kidneys
Zolmitriptan (Zomig)	Oral 2.5–5 mg Nasal spray 5 mg	• Oral Onset or action: 45–60 min, ZMT Emulation may be faster • Intranasal Onset action 15–20 min
Rizatriptan (Maxalt)	Oral 5–10 mg, may repeat in 2 h, max dose 20 mg in 24 h, MLT formulation dissolves under the tongue	• Max dose is 15 mg in 24 h it taking propranolol • Onset or action: 30–120 min, MLT formulation may be faster

SQ Subcutaneous

triptans. The standard adult dose should be tried first (sumatriptan 100 mg, rizatriptan 10 mg for instance), unless there are specific reasons why not.

The important mechanisms of action of the triptans are similar to that of the ergots and attributed to their interaction at the serotonin 5-HT receptor site. Triptans interact with $5\text{-HT}_{1B,1D,1F}$ receptor subtypes but do not have the multiple other receptor affinities possessed by ergotamines and this allows greater tolerability and improved side effect profile. The majority of clinical effects on migraine are attributable to agonism primarily at the $5\text{-HT}_{1B,1D}$ receptors. Proposed actions at these sites results in vasoconstriction of intracranial blood vessels, inhibition of release of vasoactive neuropeptides, and blocking of transmission of pain signals [3–8]. Inhibition of trigeminal transmission from first- to second-order neuron might also be very important in their mechanism of action. However, triptans are unable to block ongoing sensitization in the second order trigeminal vascular neurons, therefore they are most useful before central sensitization and allodynia has

occurred [9]. Nevertheless there is often some clinical value in treating an attack late, rather than not at all.

Bioavailability of the triptans ranges from 15 to 70% and does not appear to correlate with clinical response [10]. Triptans are metabolized by both the CYP 450 system and/or the monoamine oxidase A system. Dose adjustments may be necessary for patients taking drugs concurrently metabolized by these systems or patients with hepatic failure [11]. Naratriptan and almotriptan depend primarily on renal elimination and may require dose adjustment for patients with renal failure, but possibly are more suitable options for patients with liver failure [12].

CNS penetration also may vary among the different triptans, however this does not appear to correlate with clinic efficiency [13]. Typically triptans have a quick onset, with ranges from 30 to 60 min. In practice, it is often best to tell patients that triptans take 1–2 h for full effect and clinical trials back this up. Rizatriptan, zolmitriptan, and eletriptan appear to have a faster onset but the differences are small [10]. Alternative formulations such as subcutaneous and intranasal have slightly faster onsets of action than oral, and are advantageous for patients with rapid escalation in symptoms or who experience significant nausea. Oral dissolution formulations (rizatriptan and zolmitriptan) allow administration without water, but do not offer quicker onset of effect as they are mostly absorbed normally in the gut. Efficacy differences across different triptans have not been shown to be clinically significant [2]. However, there is evidence to support failure or intolerance to one triptan should warrant a trial of an alternative agent [10].

Triptans have few side effects. The most common adverse effect is recurrence of the migraine. Other CNS side effects such as paresthesias, dizziness, chest and throat abnormal sensations, cognitive problems, somnolence, asthenia, fatigue, nausea, flushing and myalgias may occur, depending on lipophilicity and active metabolites [10]. The side effects of chest and neck pain may be particularly concerning to the patient (see below). Subcutaneous formulations may also be associated with injection site reactions and have a higher side effect profile in general. Intranasal formulations may cause local reactions, nasal discomfort, and alterations in taste [14, 15].

There is a theoretical risk of coronary vasospasm in patients with established heart disease which has limited prescribing practices over the years [16, 17]. The cardiovascular safety expert panel had concluded in 2002, that it is safe to prescribe triptans patients with no known cardiovascular disease. Chest pain and sensations related to triptans are of unclear etiology and are not, in nearly all instances, cardiac in origin. Many etiologies have been considered including vascular pathology, esophageal, pulmonary mechanism, central mechanism, and skeletal muscle mechanisms. Action on the autonomic nervous system may be the explanation.

Since there is the potential for ischemic complications, triptans are contraindicated in patients with coronary artery disease, cerebrovascular disease, difficult to control or uncontrolled hypertension, peripheral vascular disease, ischemic bowel disease, and hemiplegic or basilar type migraine [10]. Therefore, caution should be taken when using triptans in patients who are obese, diabetic, smokers, postmenopausal women and men over 40, or patients with a strong family history of

heart disease. Avoidance in patients with hemiplegic migraine or basilar migraine comes from a time when the neurological symptoms were thought to possibly be ischemic. We now know that is not the case, nevertheless, triptan clinical studies continue to exclude these types of migraine and the contraindications remain in the package insert.

Although there is the potential for serotonin syndrome in patients who take triptans along with selective serotonin reuptake inhibitors or selective serotonin norepinephrine reuptake inhibitors, this caution has not really shown itself to be of concern, especially for triptans which are used intermittently and not daily. Other medications with serotonergic properties that are commonly used with triptans include buspirone, lithium, amantadine, tricyclic antidepressants, buproprion, trazodone, erythromycin, but serotonin syndrome has by and large failed to materialize. Material concern still exists with monoamine oxidase inhibitors however. Dose adjustments may also be necessary in patients taking concurrent triptans and other medications both metabolized by the CYP 450 pathway. Triptans should not be taken concurrently with other triptans or ergots within 12–24 h.

Concerning teratogenicity, a 2004 study found similar incidences of birth defects in babies born to mothers who took sumatriptan during pregnancy compared to unexposed mothers [18]. However, triptans remain in pregnancy 'category C' status and are generally not prescribed during pregnancy. There is no evidence of pregnancy loss, premature or preterm labor, or malformations with triptan use [10, 18, 19].

Ergots and Derivatives

Ergots were the first specific agent for abortive therapy in migraine, however with the emergence of the triptans their use has declined. In those who do not adequately respond to triptan therapy, ergotamine and ergotamine caffeine combination tablets (or suppositories) may still have a role in the acute treatment of migraine [20]. The ergot alkaloids used as abortive migraine therapy include dihydroergotamine (DHE) which has poor oral bioavailability and is given intranasally or IV/SC, and ergotamine tartrate (ET) [2]. Oral formulations of ET may also contain caffeine and phenobarbital which also contribute to their clinical effect and side effect profile [10].

The ergots exact their action at the $5\text{-HT}_{1A,1\ B,\ 1F,1\ D}$ and the 5-HT_2 receptors, which results in their effects on neurogenically induced inflammation and neuropeptide release [21, 22]. This is the basis for their anti-migraine mechanism of action. Ergotamines act on multiple other receptor types including alpha adrenergic and dopaminergic systems, which contribute more to their side effect profile [23–25].

Pharmacokinetic properties of the ergots are dependent on the formulation. Intravenous DHE has the fastest onset. Both DHE and ET are metabolized by the liver and should be used with caution in patients with hepatic failure, they are

excreted in bile [21, 23, 26]. DHE appears to have slightly better efficacy than ET but both have reported efficacy reported between 50 and 90%.

DHE is a potent anti-migraine drug that is available in SQ, IM, IV, or intranasal routes and is typically used for severe migraine attacks not responsive to other medications. The IV formulation is favored but IM, SQ may substitute in a patient with difficult IV access, and intranasal route may be used in the outpatient setting. ET is available in pill form as well as a dissolving sublingual form, multiple combinations exist. ET is also combined with caffeine, belladonna alkaloids, and/or phenobarbital.

The most common side effect of the ergots is nausea, therefore, prior to IV or SC administration pretreatment with an antiemetic is recommended. DHE nasal spray may have the advantage of a lower headache recurrence (compared to triptans) due to its longer half-life [27]. Other side effects include peripheral vasospasm, muscle cramping, tingling in the extremities, the sense of difficulty swallowing, chest discomfort, nasal congestion, and fatigue [23]. Effects on cardiac function have been reported secondary to ergot vasoconstriction properties, and should be evaluated accordingly. Although ergotamine venous vascular effects are significantly more potent than arterial, this medication should be avoided in patients with known cardiovascular and/or peripheral vascular disease [2, 23, 28].

The term *Ergotism* has been coined to describe ischemic complication of major body systems, including the myocardium as a result of prolonged or overuse of the ergots. In addition, some forms of ergotamine may produce retroperitoneal fibrosis. Another potential complication of ergotamine use is medication overuse headache [10, 23].

Antiemetics

Antiemetic medications with dopamine antagonism action has long been used in migraine treatment, and possess not just an antiemetic effect but an anti-headache effect, more pronounced in parenteral form [10, 29–31]. These agents are often mixed with other medications in abortive management and are probably still underutilized (Table 4.3). This class includes prochlorperazine, promethazine, and metoclopramide, often given orally but suppository formulations of prochlorperazine and promethazine are available and serve a very useful rescue option for

Table 4.3 Abortive management with antiemetics. They are probably still underutilized

Antiemetic	Dosing
Prochlorperazine	5–10 PO/IV, 25 mg supp
Promethazine	25 mg PO/MI/IV/supp
Metoclopromide	5–10 mg IV, 10 mg PO
Chlorpromazine	25–50 IM/PO
Ondansetron	4–8 mg PO/orally dissolving
Hydroxyzine	50–100 mg PO/IM

failed initial therapy. Intravenous metoclopramide, chlorpromazine, and prochlorperazine are used as first line in an ED.

The most common side effects are sedation and postural hypotension. However, there is the risk of akathisia and dystonic reactions. The practitioner must be able to recognize these movement side effects, not just on urgent evaluation but also by history, as the patient may not recognize that their 'anxiety' was in fact akathisia. This risk appears less so for promethazine. Diphenhydramine reduces the relative risk of akathisia by 61% and benzodiazepine administration also results in prompt resolution of this side effect [32–34].

The majority of these medications does prolong the QT interval and do increase the risk for torsades de pointes. Risk factors for torsades de pointes include high drug concentrations, medication overuse in this category, electrolyte disturbances (hypokalemia, hypomagnesemia) concurrent use with other medications which may prolonged QT interval, slow drug metabolism, and baseline prolonged QT interval. The development of QT prolongation or T wave abnormality, bradycardia, electrolyte disturbances, underlying heart disease, impaired hepatic, or renal function may necessitate an alteration of the pharmacological plan to exclude these medications, particularly so if there is heavy utilization.

Studies have shown that intravenous chlorpromazine is effective in the acute treatment of migraine [35]. Parenteral chlorpromazine treatment also improves migraine associated pain, nausea, photophobia, and phonophobia [31]. This benefit was seen in both migraine with aura and migraine without aura, and chlorpromazine treated patients had a significantly reduced rate of headache recurrence at 24 h. Common side effects included drowsiness and postural hypotension. The typical dose was 25 mg IM/IV or 25–50 mg PO.

Intravenous prochlorperazine is also effective in migraine management and is a popular treatment in the ED setting [35]. It appears to be as effective as IV metoclopramide or subcutaneous sumatriptan [36]. The typical dose is 10 mg IV given in combination with diphenhydramine to prevent akathisia or dystonic reactions. Intravenous metoclopramide has also been shown to be effective for acute migraine management [35], however less effective than chlorpromazine or prochlorperazine in relieving pain and nausea [37].

Metoclopramide chlorpromazine and prochlorperazine have been shown to work well when given IV, however there is limited data to support their anti-headache properties when given PO. For this reason, when given for outpatient abortive therapy they should be used as adjunct therapy to additional medications such as NSAIDs, triptans, or ergots [2].

Droperidol and haloperidol also appeared to be effective for the treatment of acute migraine; however, they have less of an antiemetic effect. Due to high rates of adverse events they are not considered first-line therapy [38]. Droperidol is typically given in doses ranging from 2.75 to 8.25 mg IM, but was associated with high rates of adverse events including akathisia and asthenia [39]. Droperidol does also carry a black box warning for QT prolongation and torsades de pointes. Side effects of droperidol include dysphoria, sedation, hypotension, QT prolongation, as well as extrapyramidal side effects. For these reasons, droperidol is not considered a

first-line medication for migraine. Haloperidol has also been shown to be effective for migraine pain relief but side effects occur with a substantial number of patients who receive haloperidol [40]. Typical dose is 5 mg IV or 5–10 mg PO.

Ondansetron and hydroxyzine are two additional options that offer very significant antiemetic properties. However, they do not offer much anti-headache effect and therefore should not be used as monotherapy, but as adjunct therapy with other abortive medications.

Antihistamines

Diphenhydramine and hydroxyzine may be used in conjunction with antiemetics to prevent akathisia and dystonic reactions, but also have antiemetic, anti-headache, and sedative properties of their own. It is however believed that these drugs may potentiate the headache relieving properties of analgesics, possibly by preventing further mast cell degranulation [35]. A parenteral combination of diphenhydramine and prochlorperazine have been found to be more efficacious than sumatriptan for acute migraine management [36], however oral formulations of these medications would not likely carry the same effect.

Opioids

Evidence suggests that on a whole, opioids do provide significant relief of acute migraine [41–43], however clinical trial data are limited and certain longer term concerns cannot be reflected in short studies [41]. Opioids modulate the nociceptive input to the trigeminal complex, among other mechanisms, however opioids have no effect on the inflammatory processes or neurovascular changes that occur in migraine [44]. It has also been speculated that opioid-induced hyperalgesia may be present in migraine patients [44, 45], which further questions their utility. Overall, headaches treated with opioids have a high recurrence rate [44]. Generally the propensity to increased frequency of use and tolerance are thought to be high, along with reduced responsiveness to other medications and because of this some physicians avoid opioids entirely.

Parenteral opioids may be considered, with caution, for use as a rescue medication in a medically supervised setting such as an ED. Concerns include over-sedation and conditioning to frequent ED visits. Opioids may be considered in patients who have failed multiple other therapies, or in populations in which first-line therapies may be contraindicated, such as patients with cardiac disease, pregnant women, and the elderly [10]. Common side effects of opioids include dizziness, fatigue, nausea, and drowsiness. However similar to barbiturate combinations, opioid analgesic use should be limited or avoided altogether (particularly in the outpatient setting) because of concerns for abuse, tolerance, and overuse

headache [10, 46, 47]. Practitioners who use opioids often find themselves in conflict with patients over unsanctioned dose escalation. Of note butorphanol, a mixed opioid agonist/antagonist that has been used extensively in the past as an abortive migraine medication has a high potential for abuse and should be avoided [10].

Tramadol has an opioid effect and in sometimes used for outpatient pain management including headache. Tramadol weakly binds to mu opioid receptors, but also inhibits serotonin and norepinephrine reuptake. There is a lower impact on the cardiorespiratory and gastrointestinal systems, and because of this tramadol is better tolerated than typical opioids. With regards to acute migraine management, it has been shown to be effective but studies have been limited [48]. Due to potential for overuse and side effects, tramadol is not a first-line agent. Higher doses are known to increase the risk of seizures.

Corticosteroids

Corticosteroids are used by many practitioners to treat refractory migraine with good anecdotal support, despite limited evidence. There are no good quality studies to support or refute the effectiveness of dexamethasone for termination of acute migraine, however when dexamethasone was added to standard acute migraine therapy it did reduce the rate of early headache recurrence [49], and provided no significant benefit for immediate headache relief. In that study, dexamethasone did significantly reduce the recurrence of the migraine from 24 to 72 h after a single dose. Oral dexamethasone was not found to be beneficial for preventing recurrent headaches [50]. The addition of a single dose of dexamethasone is beneficial for reducing the risk of early headache recurrence in patients treated with standard abortive therapy. The typical dose is 10–25 mg. However, this should be used cautiously, as recurrent dexamethasone use can increase the risk of glucocorticoid side effects. A course of oral steroids is often used to break a prolonged migraine episode, although there is no good quality evidence to back this up.

Isometheptene

Isometheptene is a sympathomimetic amine, with some vasoconstricting properties [51]. It is available commercially in a combination pill with dichloralphenazone, a mild sedative and acetaminophen (Midrin or Duradrin). Isometheptine has a relatively well-tolerated side effect profile, including but not limited to sedation and GI side effects. The vasoconstrictive properties (milder) can be of concern in patients with coronary artery disease or hypertension. Isometheptine does not have significantly favorable evidence [41], although most studies have been small and is a

reasonable choice in patients with mild to moderate migraine as a second- or third-line agent. In recent years, isometheptine preparations have become difficult to acquire.

Barbiturates

Barbiturate combination products have been used in acute migraine management for many years and remain popular, despite concerns about overuse. Butalbital is described as an intermediate acting barbiturate (despite a half-life of 35 h) and only ever got an FDA indication for tension-type headache. Butalbital is available in various combination forms including with acetaminophen and caffeine (Fioricet), or with aspirin and caffeine (Fiorinal) with or without the addition of codeine. Butalbital is also available without caffeine, suitable for patients who cannot tolerate caffeine. Barbiturates have several concerning side effects including central nervous system depression, intoxication, hangover, toxicity, confusion, paradoxical excitation, and effects on cognition. Currently there is limited data to support the use of butalbital in migraine patients [52]. Higher doses have also been known to produce withdrawal symptoms [53]. In addition, butalbital use has the potential for abuse and dependency problems, which may lead to medication overuse headache [10]. Extensive anecdotal experience attests to the usefulness of butalbital, likely not as helpful as triptans and can be a first-line agent in those who cannot take NSAIDs or triptans (for example, patients with vascular disease). Overuse of butalbital is likely driven more by its anxiolytic effect rather than simple rebound headache mechanisms. Although some practitioners avoid butalbital products entirely, this appears to be overly restrictive.

Benzodiazepines

Diazepam has been shown to significantly improve outcomes when combined with metoclopramide and acetaminophen [54]. Benzodiazepines may be used for their sedating effects in acute settings when further insomnia may worsen the migraine episode—simply getting the patient to sleep being the goal. Although this class may be useful, caution is advised with recurrent use due to dependence concerns.

Nonsteroidal Anti-inflammatory Drugs (Nsaids), Non-opioid Analgesics

Studies have consistently shown the efficacy of NSAIDs and other non-opioid analgesics for the treatment of migraine and associated symptoms (nausea,

Table 4.4 Placebo controlled trials and comparison trials

NSAIDs	Suggested dose
Ibuprofen tabs	200–800 mg
Aspirin tabs	600–1000 mg
Naproxen tabs	220–1000 mg
Indomethacin tabs/suppository	25–75 mg, 50–75 mg suppository
Piroxicam tabs	40 mg
Diclofenic pottassium powder for solution	50 mg
Celecoxib caps	100–200 mg

vomiting, photophobia) in both placebo controlled trials and comparison trials [10, 41, 47, 55–63] (Table 4.4). NSAIDs which have clinical trial evidence of benefit include ibuprofen [64], naproxen [65], diclofenac sodium [66], ketoprofen [67, 68], and tolfenamic acid [69]. The favorable side effect profile of NSAIDs results in first-line agent status for mild to moderate migraine attacks. Although there is a paucity of comparative studies, tolfenamic acid was demonstrated superior to acetaminophen, otherwise no significant differences were observed [41].

The proposed mechanism of action of NSAIDs includes an anti-inflammatory effect on induced inflammation which occurs during the migraine, although separate CNS effects are known [10]. NSAIDS inhibit the neuroinflammatory cascade, prostaglandin synthesis, and platelet aggregation that are associated with vasoactive substance release, all of which are processes that are involved in the initiation and propagation of the migraine [44]. Cyclooxygenase inhibitors (COX1/COX2) may also inhibit the release of prostaglandins which activate nociceptive neurons in the trigeminal nucleus, which leads to central sensitization in migraine [44, 70].

NSAID side effects have been well documented elsewhere and importantly include gastrointestinal (GI) side effects such as nausea, vomiting, gastric irritation, as well as more serious complications including bleeding, particularly in patients with a history of gastric ulcer, thrombocytopenia, platelet dysfunction, or anticoagulation. Comparatively there are fewer side effects than with an opioid or a dopamine antagonist. Contraindications include renal impairment, GI bleeding, and bleeding risk factors. NSAIDs are also contraindicated in late pregnancy.

Aspirin has been shown to be beneficial in the treatment of acute migraine [46, 71, 72]. Long-term side effects of aspirin have been well documented and caution should be used in patients who have experienced previous GI bleeding, gastric ulcers, or are on anticoagulants or other antiplatelet therapy. However in short-term trials, aspirin was generally well tolerated [41]. Overall NSAIDs and aspirin have been associated with a lower incidence of adverse events when compared to ergotamines, particularly lower rates of nausea and vomiting have been noted. Adding antiemetics to NSAID regimes often reduces nausea and other GI side effects.

Diclofenac potassium in the form of a powder for oral solution has an FDA approval for acute treatment of migraine.

Ketorolac (Toradol) has been found to be very effective for acute migraine in comparison to other agents, including sumatriptan, prochlorperazine, chlorpromazine, IV diphenhydramine, and metoclopramide [77]. Ketorolac is a COX1/COX2 inhibitor which reverses both peripheral sensitization by inhibiting the neuroinflammatory cascade in the meninges and central sensitization associated with cutaneous allodynia [44]. Typical dose is 30 mg IV or 60 mg IM.

Acetaminophen has been shown to be an effective abortive agent in some patients with acute migraine in early studies [73, 74], however additional studies have not demonstrated a significant effect over placebo [75]. The typical dose is 1000 mg and it has been shown to be effective with regards to relieving photophobia, phonophobia, headache, and improving functional disability. Acetaminophen can be used in combination with other NSAIDs and even with caffeine. It is readily available as an over-the-counter combination of acetaminophen-aspirin-caffeine, which has been found to be effective in alleviating mild to moderate migraine [76]. Overall, we would expect acetaminophen to not be as effective as a good dose of a standard NSAID.

Intranasal Lidocaine

Studies on the use of intranasal lidocaine had shown it to be effective in relieving migraine symptoms in a relatively fast timeframe, with few side effects [78–80]. Although this does typically provide rapid relief of the headache initially, some earlier studies had shown that there was a high relapse rate [80]. For this reason, this treatment is typically reserved for short term relief while other measures are being taken. Later studies had also shown that there was only marginal benefit to using Intranasal Lidocaine [81]. Overall, the evidence is insufficient to establish a definitive role for intranasal lidocaine in the management of acute migraine.

Medication Overuse Headaches

Medication overuse headache is the clinical consequence of analgesic overuse [82] This can include even the simple analgesics, along with opioids, barbiturates, triptans, and of particular note in the past-ergotamines. Daily analgesic use for any reason (other pain problems as well) can result in headache worsening, in those predisposed. Most often this is a pattern of increasing headache frequency which commonly results in daily headaches and a snowball effect whereby increasing headache frequency necessitates increasing analgesia use when the analgesics are being used for headache.

Medication overuse may be defined as the use of simple analgesics for more than 15 days per month and is also applied to the use of triptans, NSAIDS, opioids, barbiturates, or combination medications for more than 15 days in a month or less.

The 15-day parameter is a suggested number based on epidemiological studies and individuals will vary, as will expert opinion. The mechanism of medication overuse headache is not known but may be related to serotonergic dysregulation. Regardless the clinical consequence of analgesic overuse is chronic daily headache which will ultimately prevent successful treatment of the patient's primary headache disorder if not addressed. Patients may require extensive supportive care, inpatient management, and preventative therapy. Limiting the number of days per week, a patient can use abortive therapy (2–3 days a week) is thought to prevent medication overuse headache.

If medication overuse headache cannot be avoided, the offending agent should be removed immediately. Patients may require replacement with an alternative prophylactic therapy and limited abortive therapy. A short steroid taper is often beneficial when removing the offending agent. Frequent analgesic use with a careful balance between function and rebound effect is the reality for a minority of those with chronic migraine.

Preemptive Treatment

Preemptive treatment is used when a known headache trigger exists. Examples of such triggers can be exercise, sexual activity, menstruation, or high altitude exposure. Typically treatment is used for patients who are experiencing time limited and unavoidable exposures to such triggers. It has been shown that preemptive abortive therapy and daily prophylactic therapy do decrease the total number of headache days [83]. Preemptive therapy can encompass abortive medications (triptans, NSAIDS, etc.) prior to exposure to triggers, or daily prophylactic medication. Although as needed, abortive therapies prior to exposure to triggers have been shown to result in fewer adverse effects, daily prophylactic medications have shown to better reduce the number of headache days [83]. The decision to offer the patient prophylactic medications versus abortive medications depends on the individual circumstances. Frequent or severe migraine generally necessitates prophylactic medication in addition to as needed abortive medications.

Migraine Prophylaxis

While abortive therapies aim to relieve headaches when they occur, long-term therapy with prophylactic medications aims to reduce attack frequency, severity, reduce disability, improve quality of life, avoid abortive medication escalation, and overall prevent headaches (Table 4.5). Patients in general and younger people in particular are often averse to starting daily medication and even if they do not ask, many think this intervention might be lifelong. It is important to stress that need for prophylaxis will be reassessed on every visit and no decisions are being made for

Table 4.5 Prophylactic migraine medications grouped by level of evidence

Level A: Medications-established benefit	Level B: Medications-probably effective
Propranolol	Amitriptyline
Timolol	Nadolol
Metoprolol	Atenolol
Topiramate	Venalfaxine
Divalproex sodium	
Level C: Medications-possibly effective	Level U: Medications, unclear if effective
Cyproheptadine	Acetazolamide
Lisinoprol	Fluoxetine
Candesartan	Gabapentin
Carbamazepine	Verapamol
Clonidine	Bisoprolol

the very long term. Often prophylaxis is more palatable; when suggesting it should be tried for 3–5 months and then stopped to compare both on and off medication. Long-term prophylactic therapy should be tailored to the patient's individual needs, based on severity of illness, comorbidity, coexisting conditions, prior response to medications, and side effect profiles. Patients will need to be educated about their condition and its treatment and encourage participation in their own management. Prophylactic medications may also be able to guard against medication overuse headaches by preventing escalation of abortive therapy.

Prophylactic therapy should be strongly considered in patients with episodic migraine burden of greater than a couple of days per month. There are a number of medications to choose from. Generally the guiding factor on choice is the patient's comorbidities, side effect profile as well as cost and payer coverage. Recommended medication as well as their level of evidence is shown in Table 4.5. Hence one is often able to make a wise choice based on comorbidities. In the United States, the FDA has approved only five medications for preventative treatment of migraine; propranolol, timolol, methysergide (no longer available) valproic acid, and topiramate.

Botulinum Toxin (OnabotulinumtoxinA)

OnabotulinuntoxinA (Onabot) has been well studied for the treatment of episodic migraine and has been found to be ineffective [84]. Onabot has however been approved by the FDA for the treatment of chronic migraine as of October 2010 after two positive studies [85]. The benefit over placebo in the subjects studied was only 1–2 headache days a month, with an average starting headache day count at 20 per month. Hence the benefit is minimal and likely explained by factors other than a therapeutic effect of Onabot. Nevertheless, this therapy remains popular with

patients and practitioners. Chronic migraine is a very complex and difficult entity to treat, and is defined as a migraine with a headache burden of greater than 15 days per month with at least 8 days being migrainous. Typically these patients should be referred to a headache specialist.

Antihypertensives

Beta-Blockers

As a class, beta blockers are efficacious, well tolerated and appropriate first-line agents [86]. Propranolol, timolol, and metoprolol have been well studied with demonstrated efficacy for migraine prophylaxis, receiving a Level A from the American Academy of Neurology 2012 guidelines [87]. Atenolol has been shown to likely be effective in the treatment of episodic migraine, possibly not as useful as the previously mentioned. A few beta blockers including acebutolol and pindolol have not been shown to be effective, hence the benefit is not a broad class effect. Side effects include fatigue, reduced exercise tolerance, orthostasis, nausea, dizziness, insomnia, and depression. Beta blockers should be used with caution in patients with baseline low blood pressure as they can worsen orthostatic hypotension. However, the side effects are typically well tolerated and less commonly provoke discontinuation of therapy. Contraindications and cautions with this class of medications include asthma, hypoglycemia associated with diabetes, heart block, and hypotension. Beta blockers may be useful in patients with comorbid cardiovascular conditions.

Calcium Channel Blockers

Most evidence exists to support the use of flunarizine for migraine prophylaxis although unavailable in the United States. There is no significant evidence to support the use of the other calcium channel blockers in migraine prophylaxis. Studies of diltiazem and nifedipine are poor and have only suggested a modest effect. There is weak evidence to support the use of verapamil (Level U in the 2012 guidelines). Verapamil studies were small with modest effect and had high dropout rates due to side effects. Despite this, verapamil has enjoyed use beyond its entitlements. Significant side effects from verapamil can include edema, hypotension, nausea, dizziness, and constipation.

Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin Receptor Blockers (ARB)

Lisinopril has demonstrated some effectiveness in the prevention of migraine. Although a randomized, double-blind, crossover trial did show benefit when compared placebo, this was a relatively small trial. Lisinopril was relatively well tolerated with minor side effects most notably which included cough, although other side effects were fatigue, nausea, and hypotension. Other ace inhibitors have not been well studied. The angiotensin receptor blocker, losartan was evaluated in a randomized double-blind crossover study; however, this was with a relatively small number of patients. It did show modest improvement in the number of headache days when compared with placebo, as well as decreasing the severity of the headache, level of disability, and lost productivity due to headache.

Antidepressants

Amitriptyline is the only antidepressant with consistent evidence to support its use in migraine prophylaxis and the lack of FDA approval for this purpose should not be a deterrent [87]. Amitriptyline has been shown to be more beneficial in patients with mixed migraine with tension headache features, as well as in patients with comorbid insomnia. Adverse effects of amitriptyline include drowsiness, weight gain, and anticholinergic symptoms. Amitriptyline does tend to have a lower tolerability than some of the other tricyclic antidepressants, typically due to the anticholinergic effects. I the patient cannot tolerate amitriptyline a different tricyclic antidepressant may be trialed, such as nortriptyline or imipramine.

Anticonvulsants

Two anticonvulsants have FDA approved indications for migraine prophylaxis-topiramate and divalproex sodium. Topiramate has been shown in at least two large studies to be effective in migraine prophylaxis, and is often considered a first-line agent for this use [88, 89]. Given tolerability concerns, topiramate may be better thought of as a consideration after beta blockers or tricyclic antidepressants. Adverse effects with topiramate include paresthesias, nausea, anorexia, fatigue, acute angle closure glaucoma, and cloudiness of thought along with kidney stones. Adverse effects are very dose dependent. Some patients have a hard time tolerating even very small doses.

Divalproex sodium and its derivatives are well supported by evidence in the use of migraine prevention [87]. Tolerability problems are common, with the highest incidence of side effects reported for nausea, fatigue, tremor, weight gain, and dizziness. Drug levels may be checked if toxicity or compliance is ever a question.

Gastrointestinal side effects are common when starting therapy, but generally these diminish with continued use. Because of their risk of teratogenicity, divalproex sodium should not be used in pregnancy and should also be avoided in patients with a history of pancreatitis and significant liver disease.

Gabapentin has been used for migraine prophylaxis, but the evidence has been controversial and a 2013 Cochrane meta-analysis stated gabapentin was likely ineffective. Studies are limited. Significant side effects include dizziness and somnolence, and dose adjustment or avoidance with renal failure.

Magnesium and Other Prophylactic Medications

Oral magnesium may be beneficial doses greater than 600 mg per day. However, this is typically dose limiting due to diarrhea. Magnesium is however perfectly safe and often used early in those who do not desire medications or in pregnancy. Vitamin B2 (riboflavin) 400 mg daily has been shown to have some benefit at 3–4 months after initiation. However, there is limited data to support riboflavin. Coenzyme Q10 100 mg three times per day has also been shown to have some benefit in reduction of number of headache days; however studies have been limited [90]. The plant extract butterbur in the form of Petasites hybridus has level A evidence from the 2012 guidelines but more recently safety concerns (liver damage) have reduced the popularity of this natural therapy.

Pharmacological Therapy in Pregnant Patients

Management of pregnant patients with migraine is challenging, and one ideally avoids all medication, with a preponderance of caution [91]. There are many abortive and prophylactic medications which are contraindicated in pregnancy. Further, early pregnancy can worsen migraine, although the latter half, likely due to stable hormone levels, is generally much better for migraine. Pharmacologic therapy of pregnant patients may include the use of acetaminophen, opioids, corticosteroids, and antiemetics such as ondansetron and metoclopramide. Of late there have been some safety concerns with ondansetron in pregnancy, but both remain in category B. If absolutely needed, propranolol and amitriptyline have been used in pregnancy. Topiramate is best avoided (for the migraine indication). Labetalol, used in hypertensive pregnant patients, also has shown to be beneficial in migraine prevention during pregnancy. One should avoid all forms of ergotamine and caution with triptans. A closed pregnancy registry for sumatriptan use has been reassuring in finding no concern. NSAIDs may be used early in the pregnancy but are contraindicated in later trimester.

Developing a Pharmacological Treatment Plan

Developing a specific migraine treatment plan can be challenging, and as mentioned before represents the cooperative efforts of both the clinician and patient. There are a few general rules to guide in designing a treatment plan. Headaches should be treated with abortive therapies as soon as possible to help reduce the intensity and duration. Early therapy more effectively eliminates the bothersome accompanying symptoms. Failure to use abortive therapy early can ultimately increase migraine intensity, length, and overall impact of the migraine disorder and is true for all abortive therapies. Patients should be encouraged to carry around abortive medications, as needed. However, ideally such medications should be used at most 2–3 days a week. Treatments should be tailored to the individual headaches and include management of the side effects that typically accompany the migraine. The patient should always have a backup or 'rescue' plan in case abortive therapy fails. This can be a second dose of the abortive medication, a different abortive medication, behavioral therapies, and relaxation techniques or acute inpatient management. However, inpatient management should be a last resort and should only be tried after the failure of outpatient therapies and backup plans. Appropriate medications and routes of administration should be chosen for the patient's symptoms, specifically in the case of severe nausea and vomiting. Pharmacological therapy should accompany every treatment plan. When managing chronic migraine, the goals of treatment drift more to functional status and less to pain elimination. Shifting more days to mild and not impairing headache is an alternate goal in chronic migraine also.

Failure of a medication should trigger careful evaluation by the treating practitioner for errors of use, such as dose, timing, lack of repeating use, etc. Prior to considering a change of treatment there are many factors that should be examined. The clinician should assure that the patient is taking abortive therapy appropriately and as early in the course of migraine attack as possible. Studies have shown, particularly with triptans there is an increased response when treated early in the course of an attack. If the patient is not taking abortive medications as prescribed, the clinician should initiate a conversation with patient concerning the importance of abortive therapy. Other factors such as side effect profile, dose and route of administration, should also be addressed. Patients who require more rapid onset of pain relief may be better served by a nasal triptan or a subcutaneous formulation. The clinician should also ensure that the dosing of abortive therapy is appropriate and appropriate adjunct therapy is being used, i.e., patient has antiemetic agents for nausea.

When designing a treatment plan, it is important to establish reasonable goals of care and manage expectations as failure to do so on first visit is a set up for failure. The clinician may not be able to provide a pain-free result and if that is the patient's expectation, then the treatment plan may have already failed. There are numerous ways of measuring a successful treatment plan. Goals include reduction in the

number and intensity of headache days, more productivity during migraine attacks, lack of absenteeism from work, lack of ED visits, and development of coping skills.

One way to assess the overall success of the treatment plan is to assess the impact migraine has on daily life. There are a number of ways to do this, including disability outcome tools such as the MIDAS questionnaire or the HIT–6 instrument. Other specific measurements of the impact of the illness can be obtained by review of a headache diary. These may include the number of days missed from work due to migraine, lost productivity, lost family time, amount of time that is been spent incapacitated, lost leisure activities, reduced productivity, unscheduled clinic visits, or ED visits. The use of a headache diary will also allow the clinician to track migraine features. A migraine diary can include the average duration of each attack, attack frequency, which may be defined as the discrete number of headaches per month, or the number of headache days per month, response time to abortive therapies, and reduction in pain and disability from abortive therapies. This will also guide the physician when modifying the management plan.

Facilitating a partnership with the patient is something that we cannot stress enough. Patients need to not only tolerate, but also be accepting of their medication regimens, fostering adherence. This allows the clinician to accurately evaluate the effectiveness of the treatment plan prior to change. If the patient is not accepting or tolerating the treatment plan this may cause them to discontinue medical management of the migraine disorder and lead to overall frustration with the medical system.

Acute migraine management can be broken down into several stages. The choice of initial acute abortive medications should be based on severity, frequency, comorbid conditions, patient preferences, over-the-counter medication use, and past therapeutic successes. If this initial abortive therapy fails the patient should be provided with backup plan, which may include a second medication from another class or a second dose of the initial abortive medication. If the backup therapy fails the patient should have a rescue plan. This rescue plan may include barbiturates, opioids, or strong neuroleptics among other agents to provide some pain relief and ultimately avoid a trip to the ED.

Abortive Treatment Plans

As mentioned, there are two basic groups to draw from when designing abortive plans, specific medications, which include the triptans and ergots and the non-specific medications. The selection of specific medications can be difficult but some basic rules do apply. For milder migraine, which may be without significant disability, the following options are suggested; aspirin, acetaminophen, the oral combination preparation of aspirin, acetaminophen and caffeine, naproxen, ibuprofen among others. More impairing migraine (with or without aura) will likely require triptans as a first-line agent, often added to NSAIDs at the same time. Ergots should be reserved for younger patients that fail triptan therapy. Triptans should be

administered at highest available dose first, unless there is a specific reason why not. Targeting the higher dose increases pain-free outcomes.

There are numerous factors to take into consideration when selecting a triptan for migraine management, such as past efficacy, patient preference, tolerability, side effect profile, characteristics of the patient's migraine, and cost/insurance coverage. Sumatriptan is the oldest and probably most widely recognized and comes in a number of available routes. Six additional triptans are available and are recognized to have a quick onset of action; these include zolmitriptan, rizatriptan, almotriptan, and eletriptan. The onset of action of naratriptan and frovatriptan has been noted to be slower, but the duration of headache relief is likely longer. Triptan typically have similar side effect profiles namely chest tightness/pressure, difficulty swallowing and neck pain. Subcutaneous sumatriptan is noted to have a very quick and excellent outcome but also has a more prevalent side effect profile.

Both sumatriptan and zolmitriptan are available in nasal spray forms which are beneficial for patients with rapid onset migraine, or in patients with severe nausea or vomiting. Zolmitriptan nasal spray is more lipophilic and appears to have a better response than sumatriptan nasal spray formulation. Another option for patients who cannot swallow pills (at least without liquid) is oral dissolution tablets which dissolve in the mouth within a few seconds. The combination of triptans and NSAIDs appear to be more efficacious than if taken individually, demonstrated with clinical trials involving sumatriptan and naproxen.

Triptans are also indicated as a first-line agent in patients that have failed NSAIDS or other simple analgesics. They are reported to be effective in approximately 50–90% of cases of moderate to severe migraine. Again, early use and a good dose are of the utmost importance. As mentioned before, monitoring of usage is important to limit medication overuse headache. When initially prescribing triptans, it is important to educate patients as to their proper use, side effects, and to manage expectations of the medication.

The ergots are second line agents for acute migraine management. DHE is available in a number of formulations including IM, IV, SQ, and intranasal. The IV formulation is typically reserved for refractory migraine, chronic intractable migraine, or status migrainosis. DHE via the IM or IV route necessitates premedication with antiemetics. Intranasal DHE has been found to be effective for the treatment of migraine and is a viable option with a low side effect profile. Subcutaneous DHE has been shown to be slightly more effective than intranasal DHE, however patients will need to be instructed on its use. Subcutaneous DHE has not been shown to be more effective than subcutaneous sumatriptan in relieving headaches.

Ergotamine tartrate is available in both oral and suppository forms, the latter being beneficial for patients with severe nausea. ET has not been shown to be at least as effective as sumatriptan and may be associated with worsening of nausea and vomiting. Similar to the triptans, ergotamines are contraindicated in patients with coronary artery disease, hypertension, in combination with MAOI, hepatic disease, or renal disease.

For migraine accompanied by severe nausea or vomiting, non-oral routes are preferred. Patients may also benefit from oral antiemetics for symptomatic control. Overall the use of opioids and butalbital containing formulations should be limited and carefully monitored as they have a high potential for overuse and rebound headaches.

An example of a reasonable treatment plan would include sumatriptan and naproxen at the initial onset of migraine. If this first intervention fails, then a second intervention would be a second dose of sumatriptan. If this second intervention fails, the patient would have a rescue plan which might consist of a dose of diphenhydramine and oral chlorpromazine, or the very effective promethazine/prochlorperazine suppositories. Ideally treatment should forfeit the need for an ED presentation which is a last resort.

Prophylactic Treatment Plans

There are numerous options for migraine prophylaxis therapy. This should be initiated with the goals of decreasing the total disability and impact of migraine days on the patient. There are a number of first-line agents to choose from and no one agent should always be first. The choice should be made based on individual patient preferences, side effect profiles, along with comorbid conditions such as insomnia, depression, obesity, epilepsy, and raynauds phenomenon among others. Therapeutic lifestyle changes should also be incorporated in a prophylactic plan including regular meals, good sleep hygene, exercise, management of triggers, reducing caffeine and alcohol intake, etc.

Inpatient Treatment Plans

Patients that present to the ED for treatment may require a longer treatment regimen, particularly if the migraine is accompanied by nausea and vomiting. Initial treatment should consist of hydration, typically followed by one or more medications. Common initial therapy consists of either ketorolac 30 mg IM ± sumatriptan 6 mg subcutaneous (this decision will depend on whether the patient has had other triptans in the past 24 h and familiarity of the treating physicians for the triptan class), in addition to diphenhydramine 25 mg IV and an antiemetic agent. See Fig. 4.1 for suggestions on treatment. We favor parenteral prochlorperazine or metoclopramide as they have the most evidence. In addition, a dose of dexamethasone 10–25 mg may be given to reduce the risk of headache recurrence. If this treatment fails, a more aggressive option may be a DHE protocol, meaning IV DHE 1 mg q8 h with antiemetic premedication for a total of 6–9 doses to break the migraine cycle [92].

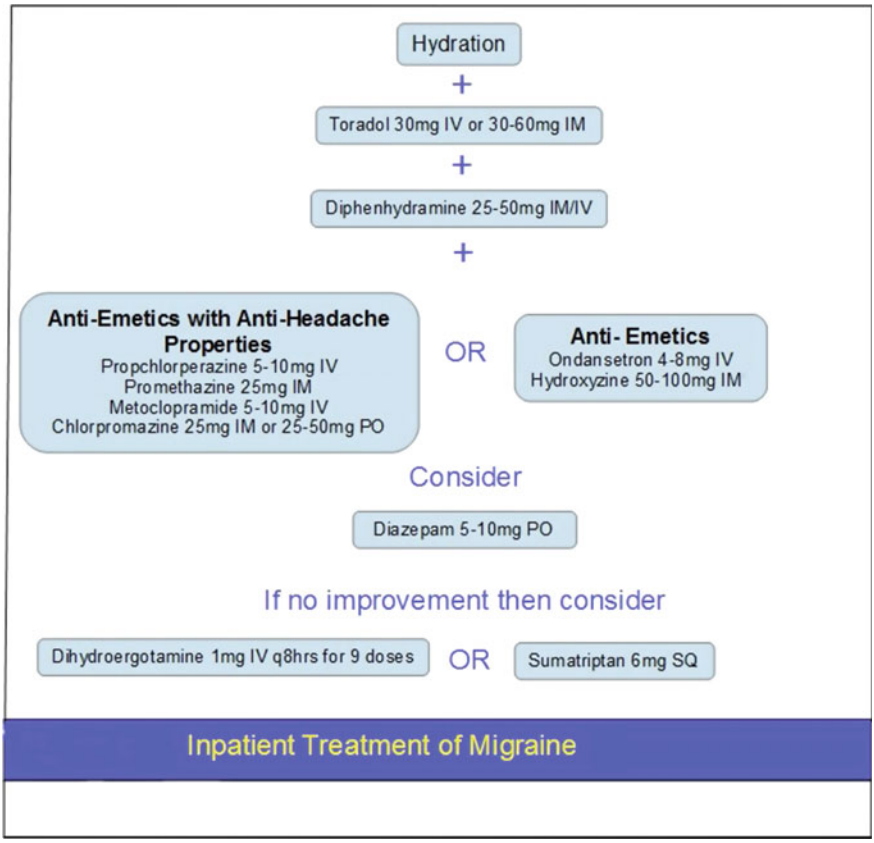

Fig. 4.1 Inpatient management of migraine

Summary of Recommendations

- There is high-quality evidence to show that NSAIDS and triptans are effective for the treatment of acute migraine.
- For mild to moderate migraine attacks, initial outpatient treatment can include NSAIDS and acetaminophen, with antiemetics for adjunct therapy as needed.
- For more severe migraine attacks, outpatient therapy should include triptans ± NSAIDs. Clinical studies do not generally support one triptan over another, however different pharmacokinetics, formulations, and other properties should guide choices.
- Prochlorperazine, metoclopramide, and chlorpromazine are effective for reducing nausea and headache, and are recommended for acute treatment in the ED. Diphenhydramine should be used as adjunct therapy to help reduce the risk of akathisia but also has anti-headache effects itself.
- Abortive therapy should be taken as early as possible.

- When designing a treatment plan, engage the patient in their own management and tailor the treatment to the individual needs. The patient should have a first- and second-line abortive treatment plan followed by a rescue plan if needed.
- A non-oral route of administration should be used for patients with significant nausea, vomiting or rapid escalation in symptoms. Subcutaneous sumatriptan and suppository medications are still likely underutilized.
- For patients that present to the hospital ED initial treatment may consist of hydration, sumatriptan, ketorolac, diphenhydramine, and a dopamine antagonist antiemetic or other antiemetic. Dexamethasone may be given to help reduce the incidence of headache recurrence. Further management should consider IV DHE (not proximate to triptan use) which may be given q8 h.

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Chapter 5
Botulinum Toxin for Migraine Headaches

David Stepnick

Introduction

About two decades ago, a local television news station ran a story about a "new" pharmaceutical being used for what to most viewers seemed to be a strange purpose —to decrease facial movement in the forehead thereby improving wrinkles associated with motion. "Why would some people have this substance injected into their bodies," the television reporter asked, "when a thimble full of this agent, in its pure form, could kill everyone in the state?" This teaser, perhaps somewhat sensationalized, was referring to botulinum toxin type A (BTX-A); the reporter ultimately was introducing this product and application to the public at a point when few people knew anything about it. BTX-A had been used by ophthalmologists for blepharospasm and strabismus since the early 1980s, but its use for cosmetic purposes, migraine, and a plethora of other indications began to expand as the general public and physicians became more aware of the product.

Improvement or elimination of migraine headaches with BTX-A were, at first, anecdotal accounts by patients who had BTX-A injected for other reasons (ophthalmologic or off-label cosmetic) or corrugator resection as part of upper facial rejuvenation surgery. Indeed, the author's first experience with BTX-A eliminating migraine headaches came in the same timeframe as did the above-noted news story. A patient handed me a sheet of paper on which was listed, in two columns filling the paper from top to bottom, a list of medications and interventions which had been tried by her and her neurologist to control her migraine headaches. "None of

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these things have really worked," she exclaimed, "but my headaches have been much better since the Botox®." My patient was receiving Botox® for her vertical glabellar creases but ultimately enjoyed elimination of what had been impossible-to-control migraines. Many thought that these reports were simply coincidences but eventually physicians and patients realized they were not isolated incidents, but rather reproducible effects that eventually led to the Food & Drug Adminstration (FDA) approval of onabotulinumtoxinA (Botox®) for chronic migraines.

BTX-A has been successfully used for a wide variety of disorders, including strabismus and nystagmus, migraine headache, smooth muscle hyperactive disorders, sweating disorders, disorders of localized muscle spasms and pain, focal dystonias, non-dystonic disorders of involuntary muscle activity, and spasticity. It is used for a variety of cosmetic purposes including for vertical glabellar creases, horizontal forehead lines, "crow's feet," to create a temporal browlift, for platysmal bands, horizontal neck lines, and by some for perioral rhytids.

History

Of the world's deadly toxins—tetanus toxin, shigella toxin, ricin toxin, aflatoxins and pufferfish toxin—botulinum toxin is the most acutely toxic substance known to man. The toxin, with a lethal dose of about 0.2–0.3 ng/kg (0.0000000002 g/kg), was first described in the 1820s by Dr. Justinus Kerner, a German physician and poet, when its toxic effects were observed after the deaths of several dozen Germans who had consumed improperly prepared blood sausages. Kerner recognized the link between the improperly prepared food and the neurological symptoms of food-borne botulism: ptosis, dysphagia, muscle weakness, and if untreated, paralysis and respiratory failure. He used the term "Wurstgift," or sausage poison [1, 2]. In 1870, another German physician, John Muller, coined the name "botulism" from the Latin term botulus, which means "sausage" or "black pudding" [3].

Dr. Emile Pierre van Ermengem, a Belgian microbiologist, first connected "the disease" botulism with a bacterium. Having discovered the bacterial causes of anthrax, tuberculosis, and cholera, he investigated three deaths and 23 cases of paralysis following a dinner at the annual gathering of the Music Society in the town of Ellezelles in Belgium. Van Ermengem's close friend had died after consumption of the salted pork dish responsible for tragedy, and his investigations led him to become the first person to isolate the microbe *Clostridium botulinum* from both the food and the postmortem tissue of victims who had died. He isolated a spore-forming gram-positive bacterium which produced the exotoxin [4]. While he named the bacterium *Bacillus botulinus*, it is now known as *C. botulinum* because of its characteristic appearance under the microscope: "kloster" meaning "spun yarn" or "thread that is twisted" in Greek.

During World War II, the US Academy of Sciences created a laboratory at Fort Detrick in Maryland for the investigation of biologic agents that could be used in

war. Potential biological weapons included botulinum toxin, already known to be the deadliest substance in the world. Supposedly, a batch of gelatin capsules filled with botulinum toxin was produced with the intent of having Chinese prostitutes slip the pills into the food and/or drinks of high-ranking Japanese officers. The project was abandoned before the plan was executed. In 1946, largely as a result of interest in botulinum toxin for biowarfare, researchers isolated a crystalline form of BTX-A [5]. This method was subsequently used by biochemist Dr. Edward Schantz to produce the first batch of BTX-A in the early 1950s.

Experimentation with the toxin continued. Physiologist Dr. Vernon Brooks discovered, in 1953, that injecting small amounts of BTX-A into a hyperactive muscle blocked the release of acetylcholine from motor nerve endings, causing temporary "relaxation" [6]. In the 1960s, Dr. Alan B. Scott, an ophthalmologist researching ways to treat strabismus, began injecting BTX-A into monkeys, theorizing that strabismus may be improved by the toxin's "muscle-relaxing effects" [7].

In 1972, President Richard Nixon signed the Biological and Toxin Weapons Convention that terminated all research on biological agents for use in war, in part responsible for the closing of Fort Detrick. Research into the use of botulinum and other food-borne toxins for medicinal use continued at the University of Wisconsin under the leadership of Dr. Edward Schantz. In 1979, he produced a "large" batch of BTX-A, named batch 79–11, which consisted of 200 mg of twice crystallized toxin. Alan Scott subsequently received FDA approval to inject small amounts of the botulinum toxin into human volunteers.

Scott published a number of studies including a 1981 paper in the *Transactions of the American Ophthalmological Society* concluding that BTX-A appeared to be "a safe and useful therapy for strabismus" [8–10]. Interestingly, as early as the 1980s, patients reported not only reduction in spasms, but improvement in facial lines. In the first half of that decade, further refinement of BTX-A as a therapeutic agent occurred as university-based ophthalmologists in the United States and Canada explored its potential. By 1985, a scientific protocol of injection sites and dosage had been empirically determined for treatment of blepharospasm and strabismus. Side effects were considered rare, mild, and treatable. The beneficial effects of the injection lasted 4–6 months.

Scott utilized a manufacturer and distributor for BTX-A which, in 1986, was not able to obtain product liability insurance. He (and others) were not able to obtain the drug and supplies of BTX-A were gradually consumed. For a period of four months, until liability issues were resolved, blepharospasm patients in the United States had to have their injections at eye centers in Canada. In 1988, Allergan acquired the rights to distribute Scott's batch of BTX-A, at that time known as Oculinum; one year later, the FDA approved its use for the treatment of both strabismus and blepharospasm. When Allergan's acquired Scott's company, it changed the drug's name to "Botox®."

Although ophthalmologists who used BTX-A for ophthalmologic indications had noticed that their patients had less severe or absent "frown lines," it was Carruthers who published a study in the *Journal of Dermatologic Surgery and Oncology* stating that, although temporary, "treatment with *C. botulinum*-A

exotoxin is a simple, safe procedure" for the treatment of brow wrinkles [11]. Still off-label in the mid-1990s, cosmetic use of Botox® increased rapidly and by 1997 the supply ran out. Once it became available again, it caught the attention of the New York Times which reported, "Drought Over, Botox is Back" [12].

In 2000, Botox® was approved for the treatment of cervical dystonia. Botox Cosmetic® was approved in 2002. Probably largely due to the attention Botox® received as a result of its cosmetic uses and the public's intrigue with a simple, non-invasive treatment for facial aging, the sales and use of Botox® skyrocketed. Physicians explored other applications for this drug, and soon the list of indications was long. These indications eventually included the treatment of overactive bladder, certain types of urinary incontinence, chronic migraine [prophylaxis in patients with migraine ≥ 15 days per month with headache lasting 4 h a day or longer], spasticity, severe axillary hyperhidrosis as well as blepharospasm and strabismus [13]. It has been used "off-label" in many different situations including for facial tics, hemifacial spasm, spasmodic dysphonia, piriformis syndrome, thoracic outlet syndrome, Parkinson's disease, myofascial pain syndrome, and for ischemic digits, among others.

Other neurotoxins were released by other pharmaceutical companies, including Myobloc®, Dysport®, and Xeomin® but none currently are indicated for migraine headaches. An FDA alert was released 8/2009 that said: "Changes to the established drug names to reinforce individual potencies and prevent medication errors. The potency units are specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to any other botulinum toxin product. The new established names reinforce these differences and the lack of interchangeability among products" [14].

As the number of anecdotal cases of migraineurs whose headaches improved after having BTX-A injected for aesthetic reasons accumulated, clinicians began to investigate using BTX-A in the migraine population. On October 15, 2010, Botox® was approved for treatment of adult patients with chronic migraine [15]. Botox® and Botox Cosmetic® officially became knowns as OnabotulinumtoxinA.

Pharmacology

Botulinum toxin is produced by *C. botulinum*, a Gram-positive spore-forming anaerobic bacterium. There are seven structurally similar but antigenically and serologically distinct neurotoxins: types A, B, C [C1, C2], D, E, F, and G. Human botulism is caused mainly by types A, B, E, and (rarely) F. The molecule is synthesized as a single 150 kD chain which is then cleaved to form a dichain molecule joined by a disulfide bridge. An approximately 50 kDa light acts, similar to tetanus toxin, as a zinc endopeptidase with its proteolytic activity located at the N-terminal end. The $\sim$100 kD heavy chain provides cholinergic specificity; it is responsible for binding the toxin to presynaptic receptors. The heavy chain also promotes light-chain translocation across the endosomal membrane.

The process of neuromuscular transmission begins with neuronal stimulation. This initiates a cascade of events that leads to the fusion of neurotransmitter-containing vesicles with the nerve membrane, a process that requires a group of proteins that are part of the SNARE complex (SNARE—an acronym from SNAP REceptor) (SNAP—an acronym for Synaptosomal Associated Protein). Membrane fusion results in the release of acetylcholine by exocytosis into a synapse. Acetylcholine diffuses across the cleft and eventually binds to receptors on the muscle, leading to muscle contraction.

BTX-A acts by presynaptically binding to high-affinity recognition sites on the cholinergic nerve terminals thereby decreasing the release of acetylcholine, causing a neuromuscular blocking effect. The effect of the toxin is permanent—the toxin does not "wear off" as it may seem to do clinically. Recovery occurs by proximal axonal sprouting and muscle re-innervation and formation of a new neuromuscular junction.

The process by which BTX-A blocks neuromuscular transmission is actually a four-step process. These steps include binding, internalization, translocation, and blocking. First, the dichain toxin complex *binds* to the presynaptic terminal, a process which takes about 30 min. Next, mediated by the heavy chain, the neurotoxin is *internalized* into the nerve cell by receptor-mediated energy-dependent endocytosis. The nerve cell actually invaginates around the toxin molecule. The toxin is then *translocated*, the disulfide bond is cleaved, and the toxin is released into nerve cell cytoplasm. The final step of BTX-A action, the *blocking* step, involves prevention of fusion of the neurotransmitter vesicle with the nerve membrane by light-chain proteolysis of SNAP-25, a cytoplasmic protein required for the attachment of acetylcholine-containing vesicles onto the nerve membrane, thereby preventing acetylcholine exocytosis.

Botulinum Toxin Preparation

Botox® is prepared by laboratory fermentation of *C. botulinum*. The toxin is harvested, purified, and crystallized. The crystallized Botox® is then diluted with human serum albumin, lyophilized, and bottled. Each vial contains 50 or 100 U of BTX-A (the human lethal dose is estimated to be approximately 3000 U). Vials should be stored in a freezer at or below 58 °C.

A 100 U vial of Botox® is usually reconstituted with saline just before use. Package insert instructions specify using saline that does not contain a preservative as the diluent, but many physicians prefer to use saline with preservative, as it seems to cause less discomfort when injected and it has the added benefit of the preservative. Solutions may be prepared with 1–4 ml/100 U vial, depending on physician preference, creating concentrations of anywhere from 25 to 100 U/ml. Once reconstituted, it should be stored at 2–8 °C. It is claimed that agitation can easily denature the Botox®, so the diluent should be gently injected onto the inside of the wall of the vial and swirled gently rather than shaken. The reconstituted

solution should be refrigerated and optimally used within 24 h. However, many physicians will use the Botox®, properly refrigerated, for several weeks. A multicenter trial, suggested that reconstituted Botox® could be effectively used for up to 6 weeks [16, 17].

Contraindications

- Patients with preexisting neuromuscular conditions (e.g., myasthenia gravis or Eaton-Lambert syndrome).
- Patients who are pregnant or actively nursing.
- Patients on medications such as such as aminoglycosides, calcium channel blockers, penicillamine, and quinine (these can potentiate the effects of botulinum toxins).

Migraine Headache

Headache is one of the most common patient complaints in a neurology office, many of these patients carrying the diagnosis of migraine headache. Headache is also among the most common complaints reported by patients visiting the emergency department [18, 19], responsible for 3 million visits in 2000, and representing an annual cost between $600 million to nearly $2 billion [20]. Estimated annual costs as a result of migraine are between $13 billion to $17 billion in the United States [21]. It has been estimated that pain costs employers more than $60 billion annually mostly from diminished job performance [22]. An estimated 6% of men and 15–17% of women in the United States have migraine headache (about 28–36 million people), causing significant disability and an impaired quality of life.

The "International Classification of Headache Disorders" describes the specific criteria necessary for the diagnosis of the many different types of headaches. For example, the diagnosis of migraine without aura must fulfill the following criteria:

(A) At least five attacks fulfilling criteria B–E
(B) Attacks lasting 4–72 h, untreated or successfully treated
(C) Headache has at least two of the following characteristics—unilateral location, pulsating quality, moderate or severe pain intensity, aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs)
(D) During headache at least one of the following—nausea and/or vomitting, photophobia, and phonophobia
(E) Not attributable to another disorder [23].

Migraine with aura has a similar set of specific characteristics used to make the diagnosis. It is very important to make sure that the headache is not attributable to

another disorder. This requires the participation of a neurologist whose expertise allows exclusion of other potential causes of headache.

The Botulinum Toxin Type A—Migraine Connection

After sporadic anecdotal observations of migraine relief in the early 1990s by physicians who were using BTX-A for cosmetic and ophthalmologic indications, by the middle of the decade many other physicians were making the same observations. Studies began to emerge that independently suggested that BTX-A is useful for the prevention/treatment of chronic migraines in adults: patients had fewer headache days, less headache-related disability, and improved quality of life.

Silberstein et al. [24] performed a double-blind, vehicle-controlled study of 123 patients with two to eight migraines per month, randomized to receive vehicle or BTX-A. Pericranial injection of BTX-A significantly reduced migraine frequency, severity, acute medication usage, and associated vomiting.

Otolaryngologists began to investigate the effect of BTX-A on headache patients in the same era. Binder et al. performed a non-randomized study at four test sites. In these 106 patients, 77 were true migraine patients. 51% of the patients reported complete elimination of symptoms; 38% reported partial response. The authors concluded that BTX-A was safe and effective for both acute and prophylactic treatment of migraine headaches [25].

Blumenfeld's study suggested that dosage was important and concluded that positive results were found when the mean BTX-A dose was 63.2 units, for a mean total treatment time of 8.6 months, during which patients received an average of 3.4 treatments [26]. Another study compared BTX-A to placebo in 60 patients. The primary efficacy point was the number of headache-free days. Statistically significant improvement in headache-free days was seen in the BTX-A group from week 8–12 [27].

Two large, random double-blind, placebo-controlled trials were published in 2005 with 702 and 571 patients, respectively, studied over a period of 11 months. There was a statistically significant decrease in the number of headache days per month in the BTX-A group compared to placebo in both studies. To see the benefit, 180 days of treatment may be necessary in some patients [28, 29].

Mathew designed an 11-month randomized, double-blind, placebo-controlled study using 13 test sites in which headache patients who had 16 or more headache days per month were treated with BTX-A. They found that botulinum toxin type A-treated patients had a decrease from baseline of 50% or greater in the frequency of headache days per month at day 180 with patients having, on the average, approximately seven more headache-free days per month [28]. Silberstein examined toxin dosages and concluded that the most benefits (compared to placebo groups) were found when patients received 150 Units of BTX-A per treatment [29].

355 patients with migraine or probable migraine were randomized in a study published by Dodick et al. in 2005. These patients were not taking other

prophylactic medication and were included in their analysis. They found, after two injection sessions, that the maximum change in the mean frequency of headaches per 30 days was −7.8 in the BTX-A group compared with only −4.5 in the placebo group ($P = 0.032$). The between-group difference favoring BTX-A treatment continued to improve to 4.2 headaches after a third injection session ($P = 0.023$) and BTX-A treatment at least halved the frequency of baseline headaches in over 50% of patients after three injection sessions compared to baseline. They concluded that BTX-A "is an effective and well-tolerated prophylactic treatment in migraine patients with CDH who are not using other prophylactic medications" [30].

Relevant Anatomy

Largely through the work of Bahman Guyuron, four "peripheral" sites have been identified that appear to be associated with and act as migraine triggers [31–37]. The first site is the glabella and forehead region, where the supraorbital and supratrochlear nerves provide sensory input implicated as a migraine trigger. The muscles in this region are primarily the corrugator muscles and secondarily the procerus and frontalis muscles. The second site is in the temporal region associated with the zygomaticotemporal branch of the trigeminal nerve and its compression from surrounding musculature. The third site is intranasal: it is the only site of the four that has no correlation with muscle tension or improvement with BTX-A. As such, this chapter will not discuss this site further. The fourth and final site is in the occipital region of the neck. The trapezius muscle and the semispinalis capitis muscles and sometimes small arteries compress or stimulate the greater occipital nerve and occasionally the lesser occipital or third occipital nerves. As with the first two sites, BTX-A injected into these muscles can weaken them ultimately resulting in improvement of migraine headaches.

Understanding the anatomy of each of these muscles is important, as placing the BTX-A in the proper position results in the desired effect while, at the same time, not causing side effects.

Vertical glabellar creases result from the action of the depressor muscles of this region: the corrugator superciliaris, the medial portion of the orbicularis oculi, and the depressor supercilii. The corrugator muscle is a brow adductor which moves the brow medially and downward. It arises from the nasal bone just above the medial orbital rim. It extends upward and laterally and inserts in the skin above the area of the middle of the eyebrow. The medial fibers of the orbicularis oculi also originate from the medial orbital rim, but anterior to the origin of the corrugator. Its fibers interdigitate with fibers of the corrugator, procerus, and frontalis muscles. The depressor supercilii muscles originate from the nasal process of the frontal bone; they insert into the skin at the medial aspect of the eyebrow. These muscles can stimulate the supraorbital and supratrochear nerves as they exit their notch or foramen and course superiorly.

The zygomaticotemporal nerve has been identified as another peripheral trigger for migraine in certain patients. The zygomatic branch of the trigeminal nerve (V_2) originates in the pterygopalatine fossa, enters the orbit through the inferior orbital fissure, travels along the lateral orbital wall, and bifurcates into zygomaticotemporal and zygomaticofacial branches (V_2 is completely sensory, emerging from the trigeminal ganglion). The zygomaticotemporal nerve passes through the deep temporal fascia about 2 cm above the zygomatic arch providing innervation to skin of the temporal area. It exits the skull in a shallow depression easily palpable about 17 mm posterolateral and 6.5 mm cephalad to the lateral orbital canthus. It communicates with the auriculo-temporal nerve and it may have accessory branches.

Another primary trigger site is the occipital region. The greater occipital nerves are the primary target of BTX-A therapy, although the lesser occipital and third occipital nerves may play a role in some patients. The greater occipital nerves are the continuation of the medial branch of the C2 dorsal root. They emerge through the semispinalis capitus in an area approximately 1.5 cm in diameter, 3 cm inferior to the occipital protuberance and 1.5 cm lateral to the midline. Janis et al. describe multiple compression points along the course of the nerve: between the semispinalis and the obliquus capitis inferior, near the spinous process; at its entrance and exit into the semispinalis; at the entrance of the nerve into the trapezius muscle, where the nerve exits the trapezius fascia insertion into the nuchal line and in the distal region of the trapezius fascia where the occipital artery often crosses the nerve [37]. Peripherally, the nerve arborizes in the subcutaneous tissue above the superior nuchal line.

Proposed Mechanisms by Which Botulinum Toxin Affects Headache

The exact mechanism by which BTX-A prevents headache has not been clearly established and still is the subject of debate. In broad terms, the development of a migraine can be thought to be a cascade of events that that ends with the headache itself. It appears that in persons who are genetically predisposed to migraines (evidence for which is accumulating), this cascade of events can be triggered by stimulation of peripheral sensory nerves which can relay pain messages to the brain.

Welch identified four components that he believed were integral to the development of migraine, of which (1) peripheral activation of the trigeminal nerve and (2) progressive central sensitization have relevance to the mechanism by which BTX-A is postulated to affect headache [38]. Central sensitization of trigeminovascular neurons appears to be an integral factor in the development, progression and maintenance of migraine headaches [39]. The headache itself is thought, to be caused by dilation of large vessels innervated by the trigeminal nerve in a cascade of events that includes release of calcitonin gene-related peptide, substance P, and neurokinin A, found in the cell bodies of trigeminal neurons [40–43].

Investigators have linked stimulation of peripheral nerves to various headache syndromes. Bartsch found a large number of neurons that had convergent input from both the dura as well as cervical cutaneous and muscle territories. Their findings support a functional continuum between the caudal trigeminal nucleus and upper cervical segments involved in cranial nociception [44]. They conclude that "The facilitatory effect of greater occipital nerve stimulation on dura stimulation suggests a central mechanism at the second order neurone level" and "this mechanism may be important in pain referral from cervical structures to the head and therefor have implications of most forms of primary headache" [44].

There probably are several mechanisms by which BTX-A controls migraine headaches. One mechanism appears to be by blocking the release of acetylcholine thereby preventing the contraction of the muscle, which stops the mechanical stimulation of potentially sensitized peripheral nerves [45].

There is also evidence that BTX-A affects not only the SNARE proteins but also decreases the release of pain mediators including substance P, calcium gene-related peptide (CGRP), and glutamate [46]. There appears to be a direct effect as the toxin blocks both substance P from trigeminal sensory afferent terminals and the release of CGRP from autonomic vascular terminals. Additionally, BTX-A inhibits the release of glutamine (which stimulates the release of substance P and CGRP [47, 48]. These pain mediators produce neurogenic inflammation and result in sensitized pain receptors, creating a feedback circuit for continuing inflammation, pain, hyperalgesia, and allodynia [47].

A third mechanism appears to be that BTX-A appears to cause an analgesic effect without paralysis when it is conjugated with lectin and applied to dorsal root ganglion cells, selectively affecting the nociceptive sensory afferents, C fibers. In the study, BTX-A attenuated nociceptive transmission in vitro and in vivo for at least 24 days [47].

BTX-A, therefore, may reduce migraine pain by alleviating painful muscle contraction, blocking the pain neurotransmitters, and interrupting the nociceptive sensory afferents.

BTX-A and Surgical Treatment of Migraine Headaches

Today, while only a handful of physicians across the United States have the training to perform migraine surgery, with its approval by the FDA, BTX-A has taken a position among neurologists in their armamentarium for control for migraines. Guyuron observed that many of his patients who carried the diagnosis of migraine headache that underwent forehead rejuvenation (which included removal of the corrugator supercilii muscles) had improvement in their headaches after the surgery. Over the past decade and a half, he has done extensive work with migraine patients and published extensively on the peripheral trigger sites and surgical treatment of migraine headache. In his early study of 314 patients who underwent this surgery, 39 carried the diagnosis of migraine. 31 of these 39 patients experienced either

complete elimination or significant improvement in their migraine headaches ($p < 0.001$) over an average follow-up period of 47 months [31]. A prospective pilot study supported the findings of the retrospective study: 55% of patients whose corrugators were injected had complete elimination of their headache and 28% had significant improvement [35]. Further anatomic investigations by Guyuron et al. led to the identification of additional peripheral trigger sites, including not only sensory nerves of the face and neck but also sinonasal trigger(s).

Guyuron proposed that it may be the mechanical stimulation of the potentially hyperexcited peripheral sensory nerves that initiates the migraine cascade and notes that in three of his [initially] four trigger sites, the sensory nerves traverse muscles, ultimately the target of BTX-A injections [31]. Guyuron analyzed his outcomes for surgical treatment of these trigger sites at 5 years and found that 88% of the 69 patients appeared to benefit from surgery after 5 years: 29% reported complete elimination and 59% noticed a significant decrease in migraine headache ($p < 0.0001$) [36].

Work-Up

Regardless of the specialty of the physician who injects BTX-A for migraines, it is important for the primary evaluation and management of these patients to be done by a neurologist. It is critical to have a firm diagnosis and to exclude other causes of headache.

As with any condition, evaluation for BTX-A injection begins with a complete history. A number of headache-specific questions should be asked including the number of migraines and headaches per month, how long they last, how painful they are, where they begin and radiate and if they are unilateral or bilateral. Additionally, questions should include at what age the headaches began, their quality (e.g., throbbing, band-like, stabbing), what makes them worse and better, and their association with other symptoms such as eyelid droop, nausea and vomiting, loss of vision, or speech difficulty. In females, whether there is a relationship between the headache and the menstrual cycle is important to establish. Family history of migraine and whether the patient had a head or neck injury are other important pieces of the history. The location where the pain *begins* can help identify the trigger site(s).

In addition to other components of a physical examination, identification of trigger sites should be attempted with specific attention to sensory asymmetries. Three of the four main trigger points are related to the trigeminal nerve (including the intranasal trigger site, which is not treated with BTX-A) and one is associated with the greater and lesser occipital nerves from C2 and C3.

Patients who describe pain over the corrugator and/or procerus can be considered candidates for BTX-A injection in the glabellar region. Those who describe pain in the region of the temporalis muscle or the zygomaticotemporal branch of the trigeminal nerve can be injected in the temporal site. These patients may also

describe puffy eyes and/or ptosis. Pain in the occipital region supplied by the greater occipital nerve may benefit from occipital injections of BTX-A. These patients may describe retro-orbital pain or "runny nose." A positive response is defined as a 50% reduction in headaches following BTX-A injection.

Nerve blocks may be used to evaluate whether or not a patient is likely to benefit from BTX-A injections (or surgery). 1.5 cc of Marcaine 0.5% plain ±1.5 cc of Kenalog-10 is placed along an approximately 2 cm line over the trapezius insertion point horizontal line, centered about 4 cm from the midline. Patients can typically point to this spot when asked where the pain is most intense.

Injection Technique

When the FDA approved Botox® for use in chronic migraine patients in October of 2010, it did so based on the placebo-controlled double-blinded PREEMPT study. As such, the approval for general use is a fixed dose protocol based upon the location of injections used by investigators in this study. Of note, chronic migraine is defined as having more than fifteen headache days per month over a three month period, of which more than eight of the headaches are migrainous, in the absence of medication overuse. "On label" use of Botox® for chronic migraines an injection of 155 units in 31 sites and will be discussed later in this chapter.

The author's technique is considered "off label" use, but it limits the amount of BTX-A used in each patient, decreases the number of sites injected and, as such, is quicker, and probably less invasive and more cost effective. Improvement in the migraine is delayed until at least the 3–10 days it takes for the muscle to be weakened but when a patient is initially being treated with BTX-A, it may take longer for the sensory nerves to become desensitized.

The Author's Injection Protocol

Glabellar Site

After providing informed consent, the patient is placed in a comfortable supine position. The patient is asked to frown or "scowl" which allows the position and extent of the corrugator to be seen as it moves the medial brow and skin creating wrinkling. The skin is wiped with an alcohol wipe. A 3 cc syringe attached to a 30 gauge 1-inch long needle is used, with a BTX-A concentration of 50 U/1.0 ml. The needle is inserted at the lateral extent of the corrugator 1 cm or more above the brow, and is passed along the belly of the muscle, becoming deeper medially near the periosteum. 0.5 ml (25 U) is injected into each side as the needle is withdrawn (Fig. 5.1). More dilute mixtures of BTX-A necessarily require higher volumes to deliver the same number of units, increasing the chances of brow depression or ptosis and are, as such, not recommended. Pressure is held briefly over the injection site.

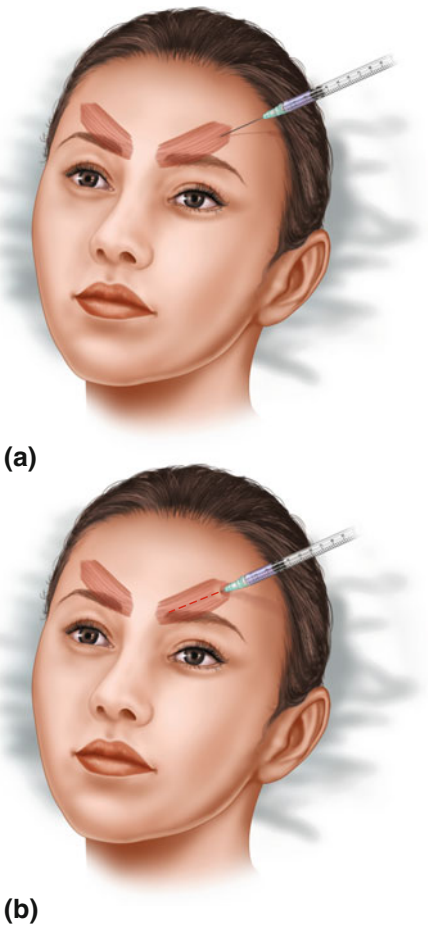

Fig. 5.1 Linear injection of the corrugator muscles is accomplished by inserting the needle at the lateral aspect of the corrugated muscle at least 1 cm above the brow, progressing deeper towards the periosteum medially, and slowing injecting the BTX-A as the needle is withdrawn

Temporal Site

As with the frontal site, the patient is placed in a comfortable supine position and, once again, a 30 gauge 1-inch long needle is used. BTX-A concentration is the same (50 U/1 ml). For the right temple, for a right-handed person, the left index finger is placed at the hollow where the nerve emerges from the deep temporal fascia, about 16–17 mm lateral to the lateral canthus. The needle is inserted about 2 cm posterior and lateral to the index finger just in front of the temporal hairline and advanced into the underlying muscle, using the entire length of the needle (Fig. 5.2). There is increased resistance as the needle pierces the deep temporal fascia and the injector should make sure that this depth is achieved. Muscle contraction may be felt. 0.5 ml of BTX-A is injected along this trajectory then cephalad, caudally, and posteriorly in an attempt to distribute the BTX-A throughout the muscle. Note that the tip of the needle should be well away from

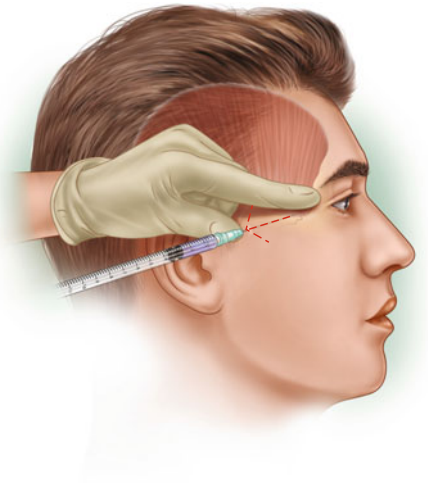

Fig. 5.2 Injection of the temporal area is accomplished by inserting the needle just in front of the hairline, passing it through the skin and fascia in a trajectory towards the shallow depression where the zygomaticotemporal branch exits. This landmark should be palpated with the opposite hand during the injections, which are fanned out above and below this initial trajectory to disperse the BTX-A in the temporalis muscle

the lateral orbital wall. Paralysis of those fibers of the temporalis muscle closest to the zygomaticotemporal branch of the trigeminal nerve is obviously most important.

Occipital Site

The patient is placed in a comfortable prone position, with the clenched fists acting as a pillow for the patient's forehead. The patient should tuck their chin which facilitates access to the occipital area. The fixed landmarks are the occipital protuberance and the posterior hairline. The patient is asked to point out, with one finger, where the pain begins; this roughly guides the site of injection. The greater occipital nerve exits 3 cm inferior and 1.5 cm lateral to the occipital protuberance and often is the site where the patient points when asked to define the origin of pain. A total of 50 U (1.0 ml) is injected 3 cm inferior and 1.5 cm lateral to the occipital protuberance, 0.5 ml per side. One is able to feel resistance as the needle passes through the trapezius fascia. It is important to use the full length of the needle, and the BTX-A should be injected in multiple passes at various angles fanning it out into the underlying muscles and almost to midline. Note that the needle is not completely withdrawn from the skin; it is almost fully withdrawn but the vector is changed, the needle is again inserted almost its full length, and this maneuver is repeated (Fig. 5.3). The depth of the posterior neck muscles are much greater than the muscles in the glabella, forehead, and temporal region and the BTX-A reaches these muscles using the 30 gauge 1-inch needle whereas it may not be using on-label techniques.

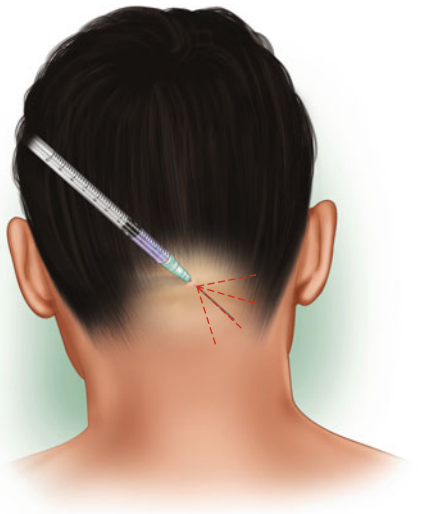

Fig. 5.3 Injection of the occipital area is done with the patient comfortably lying in a prone position, using the occipital protuberance as a landmark. An additional landmark is obtained by having the patient point to the area where pain begins. The muscles are relatively deep, so it is important to fan out the injections using the entire length of the needle

"On-Label Protocol" Injections

The PREMPT protocol involves injection of 155 U of BTX-A in 31 sites across seven specific areas of the head and neck [49, 50]. Patients undergo a trial of two treatments 12 weeks apart with subsequent treatments, if they experience improvement, every 12 weeks. Each injection is 5 U (0.1 ml). The most superficial part of the muscle should be injected, with the bevel pointing up. The entry point of the needle is not always the delivery point, as the clinician should attempt to place the BTX-A in the muscle which can be defined by inspection and palpation as the patient activates it. For bilateral sites, one side should be injected, then the contralateral site, at which point the next area is injected.

Each corrugator is injected with 5 U (0.1 ml) near the medial aspect of the brow, about 1.5 cm above the orbital rim (C—Fig. 5.4). Furrowing the brow shows the position of the corrugator as it moves the brow inferiorly and medially. Note that the corrugator originates deeply medially and becomes more superficial laterally as it inserts into the skin.

5 U (0.1 ml) are injected into the procerus, slightly beveling the needle as it is inserted, avoiding periosteum, midway between the corrugator injections (P—Fig. 5.4). The frontalis muscle is then injected, 5 U (0.1 ml) per injection in four sites, two medial injection points and two lateral injection points each side. The medial site is located by drawing a vertical line upwards from the medial inferior edge of the orbital rim in the upper one-third of the forehead, at least 1.5 cm above the corrugator site. The paired lateral injections are parallel to the medial sites, at least 1.5 cm lateral to the medial site and lining up with the lateral limbus (F—Fig. 5.4). When injections into the frontalis are too low, medial brow ptosis and/or lateral brow elevation may occur, especially in patients with some degree of

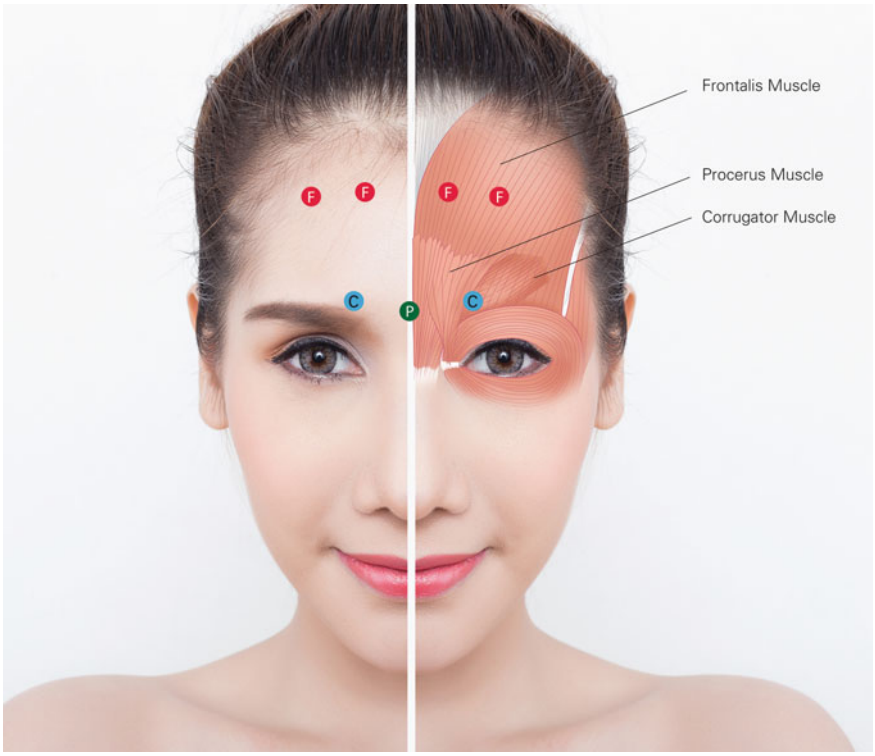

Fig. 5.4 On-label injection of the glabella region and the forehead targets the corrugator, procerus and frontalis muscles. Each injection site is injected with 5 U (0.1 ml), with a total of 10 U in the corrugators, 5 U in the procerus, and 20 U in the frontalis muscles. Details are described in the body of the text

preexisting brow ptosis. The tissues overlying the forehead are thin, as is the frontalis muscle. Injections should be superficial enough that wheal is seen after the injection.

The temporalis area receives 5 U (0.1 ml) per injection site and there are four injection sites (20 U) per side. The first site is 3 cm directly above the tragus. The second site is 1.5–3 cm directly above the first temporalis region injection site. The third site is halfway between the first and second sites, but 1.5–3 cm anteriorly (toward the face). The fourth site is 1.5 cm back from the second site, in vertical alignment with the highest point of the ear (1–4, Fig. 5.5). Prior to each injection, negative pressure on the syringe helps to insure that the needle is not within a vessel. The needle must pierce the fascia overlying the temporalis muscle, which often is felt by the injector and heard by the patient. Having the patient clenching their teeth activates the muscle and helps localize it. Pressure should be applied briefly to minimize bleeding. Note that the facial nerve is not at risk if the muscle is injected properly, as the action of BTX-A is at the neuromuscular junction;

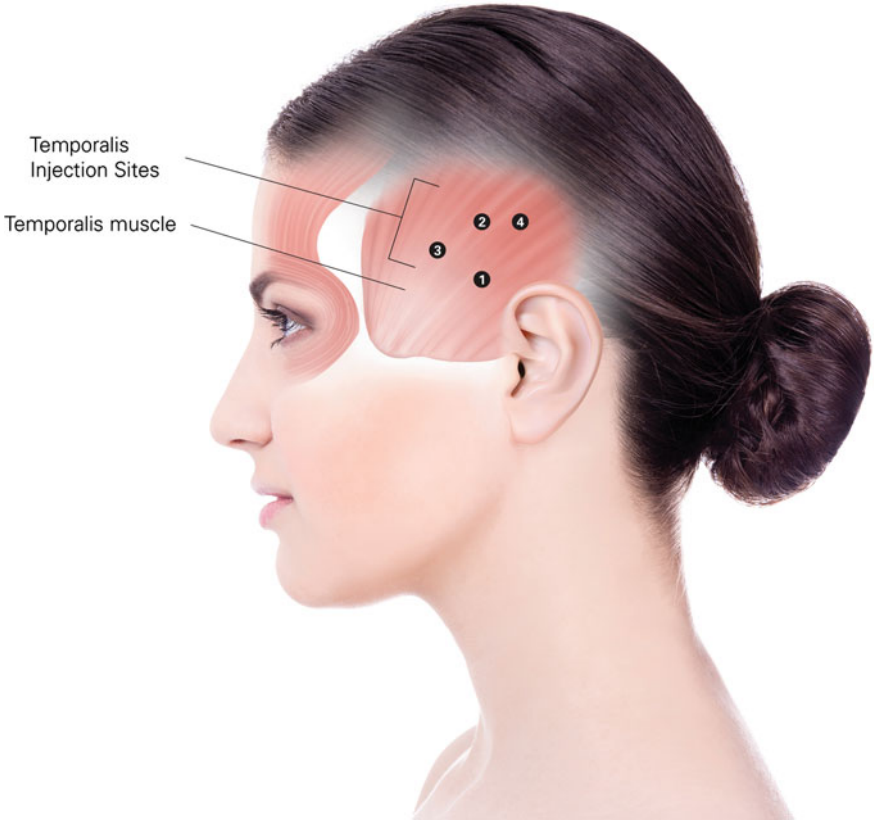

Fig. 5.5 On-label injection of the temporal region targets the temporalis muscle. As with the glabella/forehead site, each injection is with 5 U of BTX-A (0.1 ml): 20 U per side for a total of 40 U. Details are described in the body of the text

neuromuscular junctions of muscles innervated by the facial nerve are not located in this area, only the branching facial nerve itself.

Posterior injections are made in the occipitalis muscles, cervical paraspinal muscles, and in the trapezius. As with the other sites, each injection is 0.1 ml (5 U). The occipitalis receives a total of 15 U per side (three injections per side). The occipital protuberance and the mastoid process are palpated and the distance between the two is divided in half. The first injection is just above the [easily palpable] nuchal ridge at this midpoint. The second line is 1.5 cm from the first injection, along a vector from the first injection site toward the helix of the ear. The third injection is also 1.5 cm from the first injection site, on a vector medially which mirrors the lateral vector used for the second injection (O1–O3, Fig. 5.6). According to the protocol, the injections should be upwards, away from the neck, just under the dermis (which is relatively thick in this region). The cervical paraspinal muscles receive 10 U in two injection sites per side, for a total of 20 U.

The first site is 3 cm inferior to the occipital protuberance and 1 cm lateral to the midline. The second site is 1.5 cm from the first site, along a line defined by the first injection site and the helix (P1–P2, Fig. 5.6). The patient should be positioned upright, with the head neither flexed nor extended. Injections should not be lower than 3 cm inferior to the occipital protuberance and injections should be angled 45° superiorly. Finally, the trapezius is injected with 15 U per side, given in three injection sites. A line is drawn between the necklace line and the acromioclavicular joint; the first injection is in the midline of this line at the highest point of the shoulder/neck region as viewed from posteriorly. The second injection is halfway between injection site one and the acromiclavicular joint and the third injection is halfway between injection site one and the necklace line (T1–T3, Fig. 5.7).

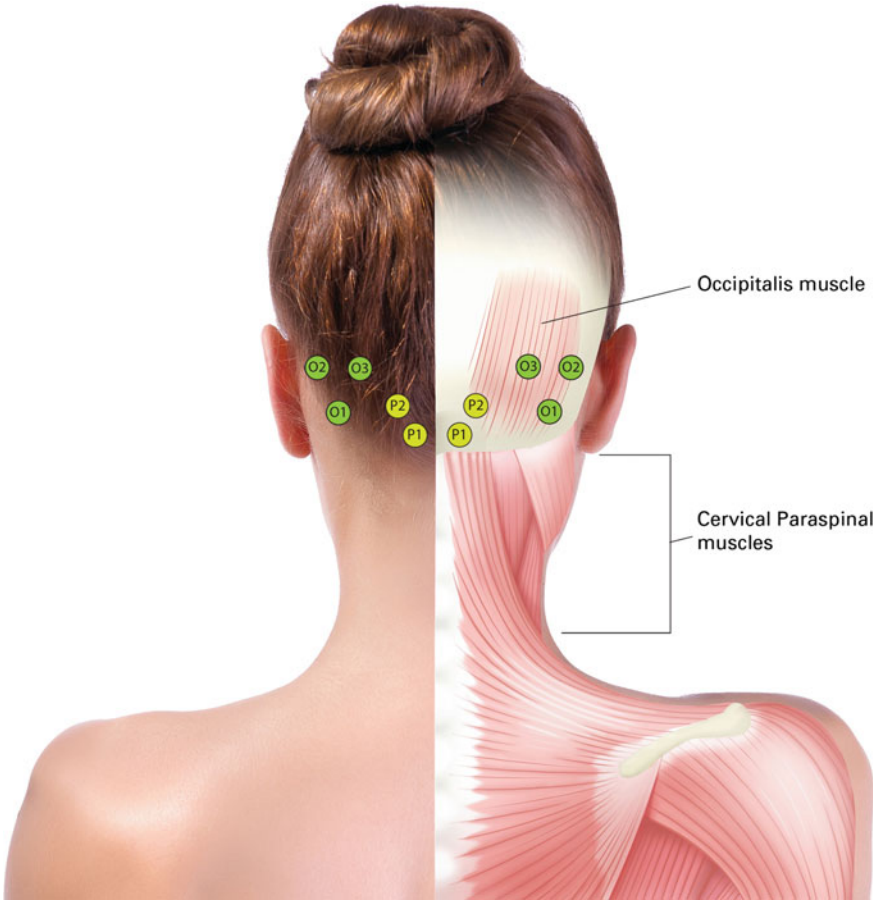

Fig. 5.6 On-label injection of the temporal region targets the occipitalis muscles and the cervical paraspinal muscles. Once again, each injection is 0.1 ml (5 U). The former muscles are injected with a total of 30 U (15 U per side) and the latter are injected with 20 U (10 U per side). Details are described in the body of the text

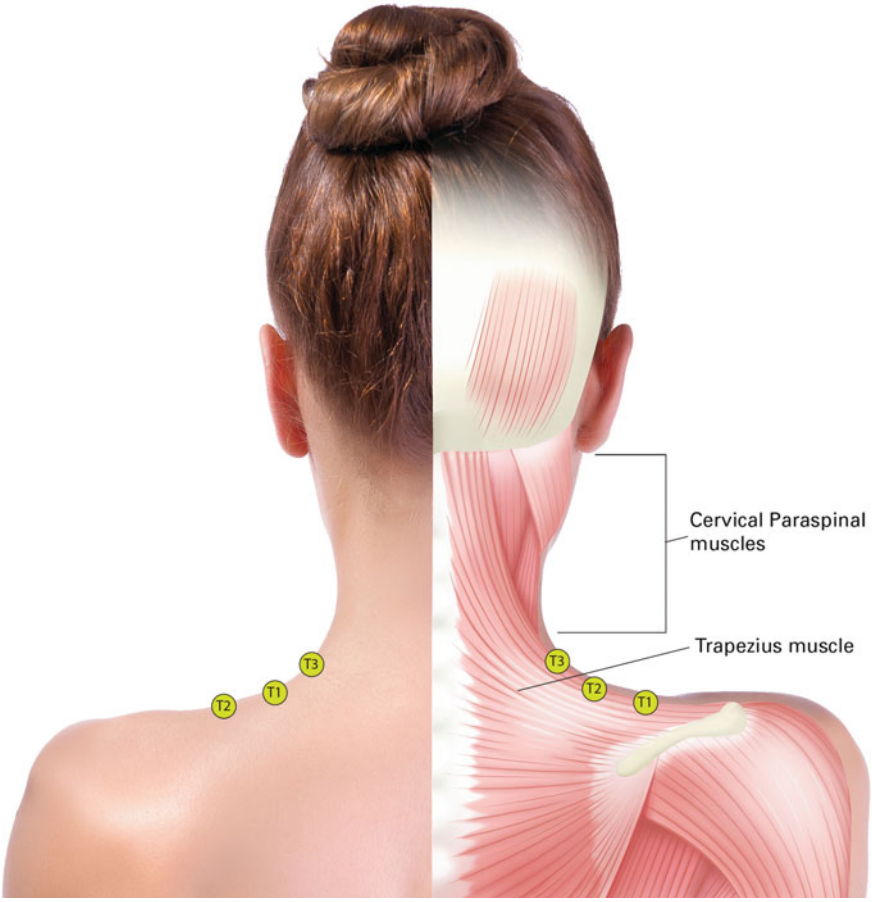

Fig. 5.7 On-label injection of the neck/shoulder region targets the trapezius muscles. As with all of on-label injections, 5 U (0.1 cc) in each site. A total of 30 U is injected into the trapezius (15 U per side)

Weakness may occur, especially in patients with small frames or patients with preexisting weakness of the neck or shoulder. Injections should be horizontal to the muscle.

Possible Complications/Adverse Effects

The clinician needs to be aware of the potential adverse effects of BTX-A before using it in their practice. Most importantly, one should be aware of the FDA'S "black box warning." The FDA warns that botulinum toxin may spread

systemically and cause asthenia, generalized muscle weakness, diplopia, blurred vision, ptosis, dysphonia, dysarthria, urinary incontinence, and life threatening swelling and breathing difficulties, hours to weeks after injection. Even though this warning accompanies each vial of the product, the FDA itself reminds us that there "has not been a confirmed serious case of spread of toxin effect when Botox® has been used at the recommended dose to treat chronic migraine, severe underarm sweating, blepharospasm, or strabismus, or when Botox Cosmetic® has been used at the recommended dose to improve frown lines" [14].

Serious adverse events have been seen with the use of unlicensed preparations that are not manufactured by Allergan. A case series of four patients with symptoms consistent with food-borne botulism had been injected with a highly concentrated, unlicensed preparation of BTX-A was published in 2006 [51]. These patients may have received doses over 2800 times the estimated human lethal dose by injection. While clinicians may be tempted to use unlicensed botulinum toxin products because of cost savings, the laboratory-confirmed cases of botulism demonstrate that without exception, it cannot be emphasized enough that only Botox® produced by Allergan should be injected.

More common adverse effects can be divided into two main categories: generalized and specific. "Generalized" effects include nausea, fatigue, malaise, flu-like symptoms, and rashes at sites distant from the injection. There have not been reports of weakness away from the injection site or central nervous system effects. "Specific" effects include injection site problems such as pain, edema, erythema, ecchymosis and short-term hypesthesia. Despite the fact that BTX-A is used for the treatment of chronic migraine, headache has been described as an adverse effect of BTX-A in injections. Discomfort is usually minimal and well-tolerated, but it can be decreased using topical anesthetics (not usually done by the author) or using small gauge needles. Discomfort can also be reduced by pinching the skin together with the underlying muscle, slowly inserting the needle bevel up and then slowly injecting the solution. Ice immediately after injection can further reduce pain, erythema, and edema. Bruising is not common but occurs most frequently in patients taking Vitamin E, NSAIDs, Plavix, or warfarin. Bruising can be minimized by patients avoiding these agents, limiting the number of injections, and applying gentle post-injection pressure. Headache is usually treated successfully by over-the-counter analgesics.

The most common complication in treating the glabellar complex is upper lid ptosis, caused by diffusion of the toxin through the orbital septum and affecting the levator palpebrae muscle. Maneuvers that help prevent ptosis include injecting at least 1 cm above the eyebrow and not injecting lateral to the mid-pupillary line. Digital pressure on the supraorbital ridge beneath the injection site can reduce extravasation inferiorly. Patients should be instructed not to push on the area that has been injected, and to remain in an upright position limit exercise for 3–4 h.

Treatment of Ptosis

When ptosis occurs, patients can be treated with Apraclonidine 0.5% eyedrops, an alpha 2—adrenergic agonist. Apraclonidine causes contraction of the Müller muscles thereby raising the lid. Ophthalmic Phenylephrine (Neo-Synephrine) 2.5% may also be used if Apraclonidine is not available.

Causes of Therapeutic Failures

In patients who have never been treated with BTX-A, failures may occur if there is a secondary headache disorder such as cervicogenic or TMJ-related headache. There may be other sites of compression. Patients may have medication overuse headache, opoid hypersensitization, abuse or addition, or even gluten intolerance.

There are a variety of reasons, in patients who previously have had headache relief from BTX-A, for therapeutic failures. Probably the most common reason is improper technique, if the injector does not have the needle in the proper intramuscular position or does not distribute the toxin throughout the muscle. The toxin may be less active, as a result of improper handling (not kept at proper temperature before or after mixing or shaking too vigorously) or error in dose or volume of the solution. A "bad batch" is theoretically possible, but probably unlikely. Circulating neutralizing IgG anti-BTX-A antibodies were thought to be important causes of failure, with earlier estimates as high as 5–15% of patients developing these antibodies; many now feel that this greatly overestimates the number of patients who are nonresponders. Risk factors for antibody production are patients who get repeat "booster" treatments after the primary injection or in patients who receive high doses (>200 U/session) of BTX-A. Tetanus toxin antibodies share homology in amino acid sequence with botulinum antibodies, so theoretically these antibodies may react with the BTX-A; cross-reactivity between the two may occur.

Marketing

There are several ways that physicians can establish themselves as clinicians who treat migraine headaches with BTX-A. The least expensive and often highest yield technique is by making established patients aware that BTX-A injections are a service you offer. Referrals by neurologists, primary care providers, and specialists such as allergists or other otolaryngologists are an important source of patients. Direct fact-to-face conversations or presentations at Departmental meetings or Grand Rounds can be useful. Patients who return to their referring physicians who have achieved relief of their migraine are likely to stimulate further referrals. Many neurologists are uncomfortable injecting BTX-A because the specialty is generally

not a procedure-oriented specialty; some neurologists are more comfortable if someone else physically performs the BTX-A injections. One cannot simply expect a neurologist to send all of their migraine patients to someone else to inject; a good relationship with mutual communication is critical.

Many neurologists are still skeptical about using BTX-A for migraines and it is important not to be lured into successfully treating headaches in a patient that has not been thoroughly, adequately, and properly worked-up. Always ensure that proper neurologic evaluation and work-up has excluded other headache sources.

Summary

Botulinum toxin type A, one of the world's most deadly toxins, once considered as a potential weapon for biological warfare, has become a commonly used pharmaceutical for a myriad of medical problems, with its list of indications growing each year. Migraine headache is a common, debilitating disease; the degree of debilitation is usually poorly understood by those not afflicted with headaches. No universally successful treatment is available so, while many other medical conditions are relatively easily controlled, migraine headache remains a difficult problem for the patients and their physicians alike. BTX-A emerged, in middle of the last decade of the last century, as a rather unlikely treatment for chronic migraine sufferers who had only achieved suboptimal control on other regimens. Since then, much has been learned about chronic migraines and BTX-A; yet, there is still a rather incomplete understanding of how botulinum toxin relieves or prevents headaches in this population. A number of investigators feel that the primary mechanism of action is by blocking the mechanical stimulation of the potentially hyperexcited peripheral sensory nerves that are involved in and initiate the migraine cascade which leads to the headache. This theory would explain the highly successful outcomes in patients who undergo surgical treatment of migraine headaches which primarily are procedures that decompress these sensory nerves. Yet, several studies have been published in the literature that offers insight into what might be additional mechanisms of action for BTX-A in patients with migraine headaches.

As experience has grown, some clinicians follow the on-label recommendations derived from the PREEMPT studies while others, through personal experience use their on off-label paradigms which have a number of advantages as detailed herein.

Recommendations

Physicians that would like to incorporate BTX-A injections for chronic migraine in their practice should always be sure that their patients have been properly evaluated and worked-up by a neurologist and have appropriate training for use of this agent. In a physician's practice that already utilizes BTX-A for other indications (e.g.,

cosmetic uses, blepharospasm, or facial spasm), it is fairly easy from a technical standpoint to adapt the injections for use in chronic migraine patients. It is more difficult to understand the "disease process" than it is to learn how to perform the injections. Those who are novice injectors probably should follow on-label recommendations and inject patients as defined for the PREEMPT study, but as experience is gained physicians may find it better to use the author's protocol detailed in this chapter. It is imperative that the physician understand how to avoid adverse events/complications and be familiar with their treatment should they occur.

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Chapter 6
Sinus Headache and Rhinogenic Headache

Mark E. Mehle

Sinus Headache and Rhinogenic Headache

Rhinogenic headache is a term that had been used interchangeably with "sinus headache" until recent studies showed that sinus headache complaints are likely to represent migraine and seldom represent sinusitis [1–3]. **Sinus Headache** should be thought of as *a patient complaint, with pain present in the sinus areas, or accompanied by nasal symptoms*. **Rhinogenic Headache**, conversely, is *a headache caused directly by pathology within the nose or paranasal sinuses* [4].

According to the 2013 *International Classification of Headache Disorders* by the International Headache Society (IHS) rhinogenic headaches are "secondary headaches" [5]. *Headache Attributed to Acute Rhinosinusitis* (see Table 6.1) is a headache with other signs and symptoms of acute sinusitis. *Chronic rhinosinusitis (CRS)* is also supported as a cause of headache (see Table 6.2). Finally, *Headache Attributed to Disorder of the Nasal mucosa, Turbinates or Septum* (Table 6.3) is described in the appendix of the *Classification*. The older term "mucosal contact point headache" was included in the appendix of the 2nd edition classification in 2004 and has now been abandoned. This term is still used extensively in the surgical literature but headaches of this nature are still considered controversial in the 2013 *Classification*.

Several recent publications have attempted to provide guidance differentiating rhinogenic headache in patients with sinus headache complaints [2, 6–8]. Perhaps the best place to start is to review the migraine diagnostic criteria, covered elsewhere in this book, and to remember that up to 88% of these patients will be found to have migraine [1].

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Table 6.1 Headache attributed to acute Rhinosinusitis [5]

Description
Headache caused by acute rhinosinusitis and associated with other symptoms and/or clinical signs of this disorder
Diagnostic criteria
A. Any headache fulfilling criterion C
B. Clinical, nasal endoscopic and/or imaging evidence of acute rhinosinusitis
C. Evidence of causation demonstrated by at least two of the following
1. headache has developed in temporal relation to the onset of the rhinosinusitis
2. either or both of the following
(a) headache has significantly worsened in parallel with worsening of the rhinosinusitis
(b) headache has significantly improved or resolved in parallel with improvement in or resolution of the rhinosinusitis
3. headache is exacerbated by pressure applied over the paranasal sinuses
4. in the case of a unilateral rhinosinusitis, headache is localized ipsilateral to it
D. Not better accounted for by another ICHD-3 diagnosis

Table 6.2 Headache attributed to chronic or recurring Rhinosinusitis [5]

Description
Headache caused by a chronic infectious or inflammatory disorder of the paranasal sinuses and associated with other symptoms and/or clinical signs of the disorder
Diagnostic criteria
A. Any headache fulfilling criterion C
B. Clinical, nasal endoscopic and/or imaging evidence of current or past infection or other inflammatory process within the paranasal sinuses
C. Evidence of causation demonstrated by at least two of the following
1. headache has developed in temporal relation to the onset of chronic rhinosinusitis
2. headache waxes and wanes in parallel with the degree of sinus congestion, drainage and other symptoms of chronic rhinosinusitis
3. headache is exacerbated by pressure applied over the paranasal sinuses
4. in the case of a unilateral rhinosinusitis, headache is localized ipsilateral to it
D. Not better accounted for by another ICHD-3 diagnosis

Table 6.3 Headache attributed to disorder of the nasal mucosa, turbinates or septum [5]

Diagnostic criteria
A. Any headache fulfilling criterion C
B. Clinical, nasal endoscopic and/or imaging evidence of a hypertrophic or inflammatory process within
the nasal cavity*
C. Evidence of causation demonstrated by at least two of the following
1. headache has developed in temporal relation to the onset of the intranasal lesion
2. headache has significantly improved or significantly worsened in parallel with improvement in (with or without treatment) or worsening of the nasal lesion
3. headache has significantly improved following local anaesthesia of the mucosa in the region of the lesion
4. headache is ipsilateral to the site of the lesion
D. Not better accounted for by another ICHD-3 diagnosis

**Note* Examples are concha bullosa and nasal septal spur

Nasal Anatomy

Branches of the trigeminal nerve provide sensation in the nose and paranasal sinuses. The maxillary (V-2) and ophthalmic (V-1) division afferents project via the trigeminal ganglion to the trigeminal brainstem sensory nuclear complex (VBSNC). Autonomic innervation of the nose is provided by sympathetic nerve fibers (originating at the superior cervical ganglion, to the deep petrosal nerve, to the vidian nerve, then through the sphenopalatine ganglion) and parasympathetic fibers (from the superior salivatory nucleus of VII, then to the greater superficial petrosal nerve, vidian nerve, and synapsing then in the sphenopalatine ganglion).

The trigeminal fibers (V-1, V-2) in the nose and paranasal sinuses terminate as bare nerve terminal endings (without specialized sensory organs) near the basal cells of the nasal epithelium, along with the parasympathetic nerves [9–11].

Nasal Neurophysiology

Nasal pain is mediated by Aδ fibers (fast responding, myelinated, primarily mechanoreceptive pain fibers) and C fibers (slower, unmyelinated fibers associated with a more dull pain from mechanothermal and chemosensory stimulation) [11, 12]. Recent studies have confirmed that the sinus ostia and the posterior-superior areas of the nasal cavity are more sensitive than other areas [13]. Referred pain remains controversial, with mixed reports after Wolff and coworkers first reported this in 1943 [14, 15].

Activation of the pain fibers is typified by the release of tachykinins (substance P, neurokinin A, neuropeptide K) and neuropeptides like calcitonin gene-related peptide (CGRP). Sympathetic neurons are associated with neuropeptide Y, in addition to norepinephrine, and the parasympathetic fibers release acetylcholine and vasoactive intestinal peptide (VIP) [11, 12, 16]. Recently serotonin (5-HT 1D) receptors have been found in nerve terminals around postganglionic cell bodies in the sphenopalatine ganglion, which may explain the reported improvement in some autonomic symptoms in migraineurs and cluster headache sufferers using triptan medications [8, 17]. Conversely, there may be local mechanisms (in addition to the expected brainstem reflexes) for nasal symptoms in "sinus headache" migraineurs.

The neurotransmitters and neurochemicals produced by the trigeminal nerves and autonomic nerves of the nose are non-specific markers of nerve activation and are associated with primary headache phenomena like migraine, as well as seemingly unrelated pathology such as allergic rhinitis, and rhinogenic pain [18–20]. None of these neurochemicals (including substance P) would be expected to confirm or refute contact point headache as a legitimate entity.

Neuroplasticity is also an established trigeminal phenomenon in which acute pain may become chronic or more easily triggered (hyperalgesia) or is temporarily *reduced*, with a temporary reduction of headache pain mediated by the VBSNC/trigeminal nucleus caudalis after any painful stimulation [11]. This may result in "false positive" results when painful stimuli are applied to validate "contact points" (see below) or may be a mechanism in which surgical pain in this area can reduce migraine headache pain, at least temporarily, even without a placebo effect being involved.

Migraine, Allodynia, and the Nose

Migraine headache is the underlying pathology in the vast majority of patients complaining of sinus headache [1–3, 21]. In addition to the pain in "sinus area" of V-2 and V-1, these patients frequently have nasal congestion, drainage, and even itching in the nose [1]. The pathophysiology of migraine is covered elsewhere in this volume, but remember that the early sensitization phase of migraine is commonly accompanied by allodynia (pain associated with ordinarily minor stimuli) in a majority of patients (80%), and typically in the distribution of V-1 and V-2 [22]. Although typically described as "cutaneous allodynia" this may include nasal stimuli, such as breathing cold air. Moreover, the migraine process itself will commonly include secondary nasal symptoms, likely from parasympathetic responses stimulated centrally at the level of the superior salivatory nucleus [1, 22, 23]. Nasal engorgement could then lead to "mucosal contact" in areas of nasal narrowing with or without allodynia-related pain. This has been suggested as supporting a potentially beneficial role for "contact point" surgery even in patients with underlying migraine [22]. This could also give a "false positive" contact point

test, where application of an anesthetic or induction of pain (injection) in the nose may down-regulate a migraine headache by interrupting a source of allodynia.

Diagnosing Rhinogenic Headaches

The diagnostic criteria for headaches related to acute or chronic sinusitis are presented in the accompanying tables, and are a very good place to start when reviewing patient symptoms and their relation to headache or facial pain. Recent evidence-based reviews have been published to assist the clinician in making the correct diagnosis [24].

Headache Attributed to Acute Rhinosinusitis (ARS)

The most common rhinogenic headache is the headache associated with acute rhinosinusitis, and the criteria for this diagnosis are presented in Table 6.1. It should be noted that the most recent (2016) ARS definitions published in the otolaryngology literature [24] are also symptom-based:

ARS is defined as sinonasal inflammation lasting less than 4 weeks with the following symptoms:

Nasal Blockage/Obstruction/Congestion or Nasal Discharge (Anterior/Posterior) and
Facial Pain/Pressure or Reduction/Loss of Smell.

They also suggest using a 10-day cutoff to differentiate a likely viral episode versus a bacterial one.

Recurrent ARS is defined as 4 or more episodes per year, and subacute rhinosinusitis is between 4 and 12 weeks duration, with the same symptoms.

Unfortunately the 2016 ARS diagnostic definition does little to eliminate migraine from the differential diagnosis—in the largest published series of "sinus headache" migraineurs, rhinorrhea was present in 40% of the migraineurs and 63% had nasal congestion [1]. In a series of other patients with primary headache disorders (mostly migraine) and no evidence of rhinosinusitis, the Sino-Nasal Outcome Test (SNOT-22) was administered, and 93.5% reported "need to blow nose" and a majority reported postnasal drainage, sneezing, nasal blockage/congestion and runny nose [25]. Other studies have confirmed an increase in congestion and nasal airway resistance during migraine attacks [23]. Clearly, many would satisfy the above definition of ARS symptomatically. The best way for the clinician to proceed would be to focus on the migraine diagnostic criteria, with particular attention being paid to the time frame of most migraine headaches—multiple episodes of 4–72 h being typical, and with substantial resolution between

episodes. Note that many of the migraineurs have pain in the distribution of V2, making the location of the pain of little value.

Chronic Rhinosinusitis (CRS)

The 2013 IHS Classification has validated chronic sinusitis as a cause of headache [5]. Several studies have looked at headache as a symptom of CRS. Unfortunately, the vast majority of these studies did not use the IHS migraine criteria in assessing these headaches, which may have led to more robust conclusions regarding the role of CRS in these headaches as a *cause* of pain as opposed to a comorbid condition. CRS is associated with a ninefold increased risk of chronic headache of any kind [26].

Regardless, the recent **CRS** definitions in the otolaryngology literature also focus on presenting symptoms [24]. The definition is sinonasal inflammation lasting more than 12 weeks, with 2 or more of the following symptoms:

Nasal Obstruction/Congestion/Blockage
Nasal Drainage
Facial Pain/Pressure/Fullness
Decrease or Loss of Sense of Smell

The authors stressed that these symptoms have a low specificity, and recommended supportive nasal endoscopic and/or imaging studies. One of these two objective findings must be present to complete the diagnosis.

CT Scanning in Diagnosing CRS, and in the "Sinus Headache" Workup

The most recent (2016) evidence-based review suggested that CT scanning is r*ecommended* in patients with CRS (by symptom-based criteria) in whom nasal endoscopic findings are lacking, or for presurgical planning. It is an *option* for confirming CRS instead of nasal endoscopy [24]. A similar review of "sinus headache" diagnosis recommended CT scanning in all patients presenting with that complaint, and recommended empirical migraine management in all patients who had negative CT scanning [6].

CT scan interpretation, on the other hand, can be wrought with difficulty. Jones [27] found a 30% incidence of incidental radiographic findings on sinus CT scans, regardless of clinical presentation. Shields et al. [28] reported no correlation between headache, facial pain, and radiographic abnormalities. Tarabichi [29] found no association between pain severity and mucosal disease in sinus headache patients and Kenny et al. [30] similarly found no correlation between headache,

facial pain, and CT disease severity. Bhattacharyya et al. [31] found no correlation between patient symptoms (SNOT-20) and CT findings, including facial pain. None of these studies addressed migraine symptoms in these patients.

Despite the difficulties correlating patient symptoms with CT findings, Anzai et al. [32] reported that CT findings considerably changed management, especially surgical management of these patients. Other studies have correlated CT scores with severity of rhinologic symptoms in chronic sinusitis patients [33]. Stankiewicz and Chow [34, 35] have presented recommendations regarding the incorporation of CT scanning in the management of the rhinology patient, as have recent consensus statements in the otolaryngology literature [24].

Finally, we must remember that migraine is a very common phenomenon, and doesn't exist in a vacuum. In one report 49 of 100 patients referred to an ENT office for sinus headache had migraine, but only 13% had migraine alone; 19 (of the migraineurs) had allergic rhinitis as well, 11 had rhinosinusitis, and 6 had both allergic rhinitis and rhinosinusitis [36]. Other studies have focused on migraineurs presenting with sinus headache complaints, finding extensive radiographic abnormalities. In one study the mean CT scan Lund-Mackay (L-M) score did not differ significantly between the migraine (2.1) and non-migraine cohort (2.7). Five of the migraine group had substantial sinus disease radiographically (with L-M scores of 5 or above), as did two of the non-migraineurs [21]. Other studies have found a history of headache in general to be more common in patients with chronic rhinosinusitis (CRS) than in non-CRS controls [37], although a second series found that facial pain (not facial pressure), headache, and photophobia were negatively predictive of the presence of radiographic evidence of CRS [38]. Finally, CRS has been reported to be a factor in the worsening of the course of migraine, potentially making it more refractory or chronic [39]. Thus, the association between CRS and migraine remains unclear.

Allergic rhinitis and migraine have been found to be comorbid as well, with some evidence suggesting that allergy management may have some headache benefits in patients with both disorders [18].

The Bottom Line—Making the Correct Diagnosis

Despite the complicated literature, there are some recommendations that can be made to guide the practitioner in making the correct diagnosis.

1. Remember that the history is the most important part of the sinus headache workup. The pattern of headache and the duration of the headache events are far more important than the treatment history, where misdiagnosis is common. ALWAYS include the diagnostic criteria for migraine in your discussion, remembering that some migraineurs may be missed but the majority will satisfy these criteria. In an otolaryngology clinic between 50 and 75% of the sinus headache sufferers will fall into the migraine category [21, 40]. Medication

history is also of great importance. Many patients will have a history of failed treatment with rhinitis medications and antibiotics. Others may have extensive use of over-the-counter (OTC) medications. The phenomenon of "chronic daily headache" may have an association with OTC analgesic overuse. Caffeine and OTC sympathomimetic decongestants like pseudoephedrine have been associated with exacerbating the course of migraine headaches [4]. Family history of migraine is important as well.

2. Proceed with a thorough rhinologic examination to look for confirmatory findings of sinusitis, as well as contact points, septal deviation, etc. Remember that sinusitis and migraine may both be present, and that the diagnosis of sinusitis does not eliminate migraine from the differential.
3. CT scanning early in the workup is recommended as a cost-effective and prudent choice, particularly in patients who have failed extensive management. These scans are crucial in making the diagnosis of rhinogenic headache, but cannot be used to exclude migraine. A negative CT scan may also guide the practitioner toward a diagnosis of mid-facial tension headache or temporomandibular joint (TMJ) syndrome if the symptomatic presentation fits these possibilities.
4. Empiric treatment for migraine is suggested in all patients who satisfy the migraine diagnostic criteria regardless of concomitant sinus disease. Some authors have suggested a trial of migraine therapy in any patient with sinus headache and a normal CT scan [6]. All diagnosed sinus disease (sinusitis, etc.) should be managed medically as well, as per published guidelines. Neurology referral at this point may be prudent as well, depending on the comfort level of the practitioner.
5. Surgery is considered a last option after *maximal medical therapy*, which includes appropriate sinonasal treatment as well as migraine management where appropriate.

Reviewing the Surgical Literature for Rhinogenic Headache

The Surgical Placebo Effect

Any discussion of surgical intervention for headache requires a review of the literature, and a careful consideration of the placebo effect in surgical studies. Surprisingly, the placebo effect has seldom been discussed in the otolaryngology literature despite its importance. A 2014 review [41] of the use of placebo controls in surgical studies found that in 74% of the 53 placebo-controlled trials reviewed, there was improvement in the sham surgical placebo arm, and that in 51% the placebo effect didn't differ from the actual surgical arm. The authors felt that this was evidence supporting the long-held belief that the placebo effect is stronger in invasive interventions as compared to non-invasive ones, particularly if

accompanied by the appearance of a confident diagnosis and a decisive approach from the treating surgeon [41–43]. Often, in studies the actual surgical effect was generally small compared to the placebo. The placebo arm may also show a surprisingly large effect, referred to as a "megaplacebo" with an effect size of >0.8. This megaplacebo response was found in greater than half of the placebo arms in a second review of minimally invasive surgical procedures [44]. This may reflect a response to the level and conviction of the surgeon's recommendations as well as the impression of a procedure as being "advanced". Ironically, these minimally invasive procedures are prime for problems with lowered thresholds for utilization or application to a wider series of complaints, referred to as "indication creep" [44]. *Indication creep* is a term that one may want to keep in mind as sinus surgery technology is expanded to include efforts to resolve "sinus headache" complaints.

In general terms, one must consider a "true" placebo effect along with other factors adding to an apparent placebo effect. These factors include the natural course of disease (e.g. improvement of migraine spontaneously over time), unidentified parallel interventions (e.g. patients in a surgery study using non-study medications), time effects (e.g. patient and investigator skill and expectations over time), and the phenomenon of *regression towards the mean* [45]. The latter phrase, although frequently misused, is essentially the concept of variability of intensity of a symptom (e.g. headache) over time. Natural fluctuations are expected to occur, and the patient may start at a "peak" symptom level at study entry, and a natural return to an "average or mean" symptom level will give the appearance of improvement. It is the natural tendency for patients to seek care when their symptoms are at their peak – a particular likelihood in surgical headache-oriented studies.

There is also the phenomenon of neuroplasticity, addressed earlier, where the pain of intervention may result in a down-regulation of headache, regardless if the intervention itself was responsible physiologically [11, 46].

As far as the "true" placebo effect is concerned, studies looking at headache are of particular concern. Researchers have found that the placebo effect on pain is greater than on other symptoms, and may even be associated with activation of central nervous system pain centers and release of endogenous neuropeptides including opioids and cannabinoids [47]. *Cognitive dissonance* is another contributing factor—the tendency for a patient who has subjected himself to a painful or inconvenient procedure to be subconsciously motivated to report benefit [48]. This will certainly contribute to the benefit reported in both the placebo and active treatment arms.

Unfortunately, when one reviews the sinus headache surgical literature, one rarely finds a sham surgical arm, and factors such as patient self-selection for surgery are common. The frequent reporting of mean results makes determination of an effect size nearly impossible, particularly when dealing with subjective measures such as pain. Thus, the results of surgical intervention for rhinogenic headache may indeed be "too good to be true" and need to be reviewed with scrutiny.

Surgical Intervention for CRS-Related Pain

Soler et al. [49] described headache as the "most disabling" symptom in 29% of their CRS patients undergoing FESS, but no evidence of post-operative headache improvement was found. Chester et al. [50] published a meta-analysis of published series of FESS patients with CRS, and found that among all of the symptoms analyzed (nasal obstruction, facial pain, postnasal discharge, hyposmia, headache) all of the scores improved postoperatively, but headache scores improved the least. Other studies have reported a more substantial improvement with surgical intervention, and several recent studies are presented in Table 6.4 [49–59]. Taken as a whole, the effect of appropriate sinus surgery on the headaches of a CRS patient can be expected to be variable, and somewhat unpredictable. As such, a few general recommendations can be made:

1. Patients need to be informed that their headache complaints are the least likely symptoms to be resolved by sinus surgery.
2. Headache alone should be considered a disincentive for sinus surgery unless other symptoms are present, and should be thought of as a last resort.
3. Further study is needed to determine whether headache resolution is an effect of surgery, or if this apparent improvement is the result of factors such as placebo effect, neuroplasticity or regression towards the mean (see above discussion).

Table 6.4 Surgical intervention for headache in CRS, using functional endoscopic sinus surgery (FESS)

First author	Year	Headache outcome
Chow	1994	82% improved
Clerico	1997	79% improved
Parsons	1998	91% improved
Ramadan	1999	60% improved
Tarabichi	2000	62% improved
Giacomini	2003	67% improved
Levine	2004	74% improved if other sinus symptoms present, 18% if headache was only symptom
Moretz	2006	Significant reduction in mean headache score
Phillips	2007	79% improved
Soler	2008	No significant headache reduction
Chester	2009	Meta-analysis, 21 sinus surgery studies, over 2000 patients, headache was the least likely symptom to improve after FESS

References [49–59]

Mucosal Contact Point Headache

Sluder (1908) described a syndrome of recurrent hemifacial/hemicranial pain with secondary parasympathetic symptoms (likely cluster headache in retrospect). This headache type was later coined "contact point" neuralgia, although the original description didn't stipulate mucosal contact of any kind [60].

In recent years, contact point headache has remained a contentious concept. Abu-Bakra and Jones, for example, found that neither local pressure in the nose nor the application of substance P to various points in the nose in 10 volunteers produced referred pain to the face or headache [15]. "Success" is also defined differently from study to study, with little standardization, often referring to frequency, intensity, duration of symptoms, or even reporting mean scores for groups of patients. As noted in the section on surgical placebos, the calculation of actual effect size, if any, is very difficult.

Radiographically, contact points are common on sinus CT scans but correlate poorly with facial pain or headache. In a study of 973 patients referred for a sinus CT scan, the incidence of radiographic contact points was 4%, and didn't differ among those patients with or without facial pain complains (42% of the patients) and had no correlation with sidedness in patients with unilateral discomfort [61]. Other studies have shown a much higher incidence of contact points (up to 55%), but no association with facial pain or headache has been proven [62]. Headache causality has little relation to the presence or nature of the contact when present.

There may be little correlation between CT findings and outcomes of minimally invasive endoscopic sinus surgeries conducted for "rhinogenic headaches." One study used radiographic criteria such as "contact points" and concha bullosa as inclusion criteria for surgery in 33 sinus headache patients and reported a surgical success rate (headache improvement or resolution) of 84.8% after a mean follow-up of over 18 months. Interestingly, all of their *failures* had clear septal spurs, and they noted no association between "contact points" and surgical outcomes [63]. Often, in these "positive" studies the patients still have some headaches, which would seem to refute the entire concept of "contact point" causation [46].

Despite poor anatomic and physiological correlation, contact points remain a surgical target for "sinus headache" complaints. Part of this support stems from the use of in-office anesthetic testing. In a study by Goldsmith et al. cocaine was used to anesthetize the apparent contact point. A "positive" response (i.e. resolution of an active headache) was used to support surgical intervention [64]. Similar testing has been suggested using injected lidocaine, or topical anesthetics of various kinds. Using a topical anesthetic, Ramadan found no correlation between a positive test in the office and improvement of headache after surgical contact point resection, citing an approximately 60% improvement either way [54]. Similarly, Abu-Samra et al. [65] (see below) found no correlation between a positive local anesthetic test and patient satisfaction after contact point surgery, although *complete* headache resolution was more common in anesthetic responders. The most recent IHS guidelines

for the diagnosis of *Headache Attributed to Disorder of the Nasal mucosa, Turbinates or Septum* support the use of this test, regardless of validity [5].

Abu-Samra reported 42 patients who underwent septoplasty with or without endoscopic partial turbinectomy for contact point headaches and chronic daily headache, in the presence of chronic migraine (20 patients) or chronic tension-type headache (22 patients) using IHS criteria. They reported a reduction of mean headache days per month from 22 to 7 [65]. Again, the use of average scores and lack of complete resolution makes interpretation of this sort of literature difficult.

Other studies have reported success despite primary headache disorders or using a combination of sinus surgery as well as contact point resection, again with reports of some benefit. A summary of recent studies is presented in Table 6.5 [65–74].

To summarize, the contact point studies may be supportive of a role for surgery for some patients, but all are evidence-based medicine (EBM) level 4 evidence [6]. Diagnostic/inclusion criteria, follow-up, surgical technique and comorbidity (primary headache or otherwise), are inconsistent. It should be remembered that issues like regression to the mean, neuroplasticity and cognitive dissonance may explain the improvement as well as a placebo effect [46]. Clearly randomized, controlled studies would be the best method to try to resolve this contentious issue, and surgery should be thought of as a last resort in these patients, many of whom may not have a truly rhinogenic headache.

Concha Bullosa–Related Headache, Middle Turbinate Headache

In addition to contact points, middle turbinate pneumatization (i.e. concha bullosa) has been incriminated in the etiology of headache. Concha bullosa may be found in up to 50% of middle turbinates [75]. Goldsmith et al. reported their experience with

Table 6.5 Surgical intervention for apparent nasal contact point Rhinogenic headache

First author	Year	Headache outcome
Novak	1992	78.5% Complete resolution (n = 299)
Tosun	2000	90% improved (n = 30)
Sindwani	2002	54% cured (n = 13)
Welge-Luessen	2003	65% improved (n = 20)
Behin	2005	>90% improved (n = 21)
Mokbel	2010	62% symptom free (n = 120)
Betkas	2010	57% complete relief (n = 36)
Moehebbi	2010	83% improved (n = 36)
Yazici	2010	Significant mean improvement (n = 38)
Abu-Samra	2011	62% improved (n = 42)

References [65–74]

middle turbinate headache syndrome, noting that contact with adjacent mucosa (with or without concha bullosa) was present in these patients. All patients had headaches lacking an aura, and no response to ergotamine therapy. They reported that 6 out of 6 subjects improved with middle turbinate surgery, which included FESS and septoplasty if they felt it was indicated. Two improved with medical management alone [64]. Like many studies on this topic, there was no randomization or control group, no screening for migraine headache, and follow-up was variable. Other studies have failed to find an association between concha bullosa and sidedness of headaches [21].

Despite this, there are many studies in the international rhinologic literature that express enthusiasm for middle turbinate or concha bullosa resection in headache patients. Roozbahany et al. [76] described concha bullosa in in almost 30% of their rhinogenic contact point headache patients, noting that it is the most common cause of this entity. Septations in the concha bullosa seem to be clinically irrelevant [77]. Cantone et al. [78] in 2014 randomized a series of 102 concha bullosa patients with headaches to receive surgical or medical management (fluticasone nasal spray), and demonstrated significant improvement in headache severity and discomfort scores using visual analog scales and the migraine disability score (MIDAS) in the surgical cohort as compared to those managed medically.

Kunachak [79] described in-office middle turbinate lateralization in 55 patients based on anatomic findings and response to topical lidocaine. All had "complete responses" although 7 of them (13%) required a second procedure. Randomization, medical management and primary headache disorders were not discussed [79]. A similarly enthusiastic study reported success in headache patients with partial resection of a pneumatized middle turbinate if they had pain on palpation of the superior and medial orbital rim (Ewing's and Grunwald's points, respectively) implying pain of a "secondary origin" [80]. Studies of this nature are common in the recent literature ([79–82] see Table 6.6) but are of questionable scientific validity due to the lack of controls, sham surgical options, lack of blinding, and frequently poor long-term follow-up.

Table 6.6 Surgical intervention for middle turbinate/or concha bullosa headaches

First author	Year	Headache outcome
Sanges	2011	100% improvement (n = 26)
Yarmohammadi	2012	Significant reduction of mean headache severity, duration and frequency compared to non-operated controls (n = 44)
Cantone	2014	Significant reduction of mean headache severity scores compared to non-operated controls (n = 102)

References [78, 80, 81]

Surgery for Migraine Relief?

Although "migraine surgery" is covered elsewhere in this volume, it is important to realize that reports have suggested rhinologic triggers in some migraineurs may benefit for surgical intervention. Behin [70] and Abu-Samra [65] have independently reported success with contact point resection in documented migraineurs. Guyuron and coworkers have also noted that intranasal surgery may provide a benefit to migraine sufferers unresponsive to medications, but all of these reports suffer from the same drawbacks mentioned for contact point surgery in general.

In the 2011 Guyuron migraine series (see Chap. 9 for detailed discussion) 69 surgical patients (88%) had a positive response (reduction of the frequency, duration, and intensity of headache). Fifty-two out of the 69 underwent septoplasty or partial turbinectomy in this series, but only 3 underwent nasal surgery alone [83]. It was later reported that in patients with "nasal triggers" alone only 3 out of 6 patients in their updated series [84] had a favorable response, a response rate far lower than the remainder of their patients.

Finally, Yazici et al. [74] reported rhinologic evaluations in 99 patients with primary headache, 70 of which had migraine. Seventy-three of the 99 were found to have rhinoscopic findings such as turbinate hypertrophy, contact points, or concha bullosa. Significant reduction of headache severity was reported in the 38 subjects who opted for surgery out of the 53 subjects who were described as "not responding to medical therapy" [74].

The Bottom Line: How to Interpret the Rhinogenic Headache Surgical Literature

The literature regarding sinus headache surgical interventions is rather contradictory. Some studies show tremendous success rates or enthusiastic endorsements for intervention, while other reports completely contradict these studies, or point out the extensive problems with study design, inclusion criteria and follow-up. As will be obvious reading this chapter, one should start with a review of the placebo effect in surgical studies, and the lack of a rigorous scientific approach in trying to elucidate the nature of the surgical response, if any. All practitioners are united in wanting to help these patients, who are frequently seeing a specialist after years of unsuccessful management. Perhaps the best things we can offer these patients are the following:

1. A correct diagnosis based on knowledge of migraine, medical headache, and sinusitis diagnostic criteria. We need to remember that a correct diagnosis follows these ***symptom-based*** criteria (according to both the neurology and the otolaryngology literature) and does ***not*** follow rhinoscopic or CT scan findings, where sinus thickening, contact points or concha bullosa may have no correlation with headache causality [85]. This may be the most difficult step for

young practitioners learning to manage these complex patients, particularly with our focus on technology in otolaryngology and allergy.

2. An emphasis on patient advocacy. Patients need to be fully and realistically informed about the yield in headache response with surgical intervention, and the importance of exhausting all reasonable medical options first. There is a tendency among all of us to desire an easy, quick fix to a problem, and we must remind ourselves to consider all alternatives appropriately. The literature surrounding sinus headache surgical intervention is enthusiastic but unscientific. We also must make every effort to avoid the "indication creep" that may occur when surgical intervention becomes more convenient or less painful. In-office sinus procedures are already being marketed directly to patients for headache relief, and we need to remain scientific and objective when dealing with these frustrated patients.
3. Finally, there is a need to push for a more scientific basis for the study of surgery for headache. The lack of randomization and controls in most of the available literature is understandable but this makes decision making much more difficult. There is a push internationally for the inclusion of surgical placebo arms in these studies, and the future may finally hold solid scientific evidence regarding intervention in these headache sufferers. As a specialty, we must insist that this actually happens.

Summary and Conclusions

In summary, "sinus headache" complaints and rhinogenic headache are two different entities: the former is a patient presentation which frequently is found to represent migraine, and the latter is a concept where nasal or paranasal sinus pathology are believed to be responsible for facial or head pain. Mucosal contact point as a source of headache remains contentious, despite an enthusiastic but largely unscientific body of literature supporting it. The association between sinonasal disease and migraine headache is also in need of elucidation. Diagnosis in these patients should be symptom-based, with rhinoscopic and radiographic evidence providing a supportive role. Intervention is primarily medical, with surgery used as a last option.

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Chapter 7
Allergic Rhinitis and Migraine Headache

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Introduction

Allergic rhinitis (AR) and headache are very widespread and common health conditions with a significant healthcare burden. As an entire spectrum, headache disorders may affect up to 50% of the global population at any given time, whereas chronic migraines affect between 2% and 5% of chronic, daily headache sufferers [1–3]. Similarly, allergic rhinitis has prevalence rates as high as 30% in adults and up to 40% in children, with some variations internationally. The socioeconomic and cost implications of these disorders are considerable, but far more significant are their impact on patient quality of life. In clinical practice, many patients present with "sinus headaches" that are, in fact, found to be headache disorders or migraines [2, 4]. The term sinus headache represents a symptom complex, and does not accurately describe an underlying pathologic process. These patients have often already undergone a multitude of diagnostic workups and treatments, including systemic and topical medications, immunotherapy, and surgical procedures. The diagnostic challenge, in part, is due to the lack of an accurate or standardized clinical definition of "sinus headache." The term is generally applied to the description of pain or pressure emanating from the periorbital, maxillary, or frontal regions. A strictly rhinogenic headache results from pathophysiology that is

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centered in the nose with headache or facial pain as a secondary effect [5]. In some cases, autonomic symptoms accompany such complaints, which are also present in migraine.

While headaches can result from sinus inflammatory disorders, including chronic or recurrent bouts of sinusitis, up to 90% of purported sinus headaches actually fulfill the diagnostic criteria for migraine [2, 4, 6–9]. Furthermore, of those patients referred to an otolaryngologist specifically for sinus or nasal inflammatory conditions, up to 75% are ultimately found to have migraines [10, 11]. Contrary to popular belief, sinonasal inflammatory conditions are usually not a direct cause of headache or migraine disorders. Despite the presence of both conditions in many patients, migraine and allergic rhinitis remain separate entities with similar components within their pathophysiological mechanisms.

Pathophysiology of Allergic Rhinitis

The basic concept of allergic rhinitis, a subset of atopic disease, is that an individual's immune system inappropriately reacts to a benign substance, the so-called allergen, and induces an inflammatory response that manifests primarily in the nose. Allergic rhinitis is largely driven via immunoglobulin E (IgE) dependent mechanisms [12]. Once the allergen contacts nasal mucosa, antigen presenting cells (APCs), primarily dendritic cells residing in the mucosal surface, process the allergen and present peptides via major histocompatibility complex class II molecules to CD4 T cells [13]. This interaction induces secretion of chemokines CCL17 and CCL22 from the dendritic cell that along with IL-4 present from basophils, activates the transformation of the naïve T cell into a Th2 cell [12]. Th2 cells secrete cytokines IL-4, IL-5, IL-9, and IL-3 that recruit eosinophils and activate B cells to produce allergen-specific IgE antibodies [12, 13]. IgE itself then activates proliferation of eosinophils, mast cells, and neutrophils, and the allergen/antigen specific IgE subsequently binds to high affinity receptors on mast cells or basophils for later activation [13]. These bound allergen-specific IgE are part of the body's retained memory of the allergy that leads to quicker immunological response with subsequent exposures. The process of mast cell granulation and eosinophil inflammation is postulated to have evolved to just kill parasites, but then extended to react inappropriately to items which the immune system should view as innocuous (i.e., allergens) [12].

Early and Late Reactions

Following exposure to allergens, allergic rhinitis sufferers develop two different reactions according to time sequence. The early reaction occurs within 30 min of exposure and is characterized by sneezing and rhinorrhea [13]. The

pathophysiological mechanism involves degranulation of mast cells once bound IgE links with an allergen peptide (type I hypersensitivity) with release of chemical mediators like histamine, prostaglandins, and leukotrienes [13]. Mast cells are maintained by IL-9 and stem-cell factor [12]. The late reaction occurs approximately six hours after exposure and is characterized by nasal congestion [13]. The main pathophysiologic mechanism involves chemotaxis of eosinophils which is the result of a cascade initiated during the early reaction. Cytokines and chemokines attract eosinophils, mast cells, and T cells to the nasal mucosa causing congestion, cell breakdown, and eventually remodeling of normal nasal tissue [13]. In addition, destruction of the nasal mucosa exposes embedded distal branches of the trigeminal nerve to cytotoxic proteins from eosinophils. In turn, these damaged sensory nerve fibers then secrete neuropeptides including substance P, neurokinin A, and calcitonin gene-related peptide (CGRP), which induce contraction of smooth muscle, mucous secretion from goblet cells, and plasma exudation from capillaries, a process known as neurogenic inflammation [12, 14]. Additionally, inflammatory mediators like bradykinin and histamine activate unmyelinated C fibers [12]. These processes produce the symptoms of nasal congestion, rhinorrhea, nasal itching and sneezing, and overall hypersensitivity to specific allergens as well as stimuli such as cold and dry air, tobacco smoke, and tactile pressure [13].

Suppression of the Allergic Response

Regulatory T cells (Tregs) inhibit cells involved in the allergic inflammatory cascade by directly secreting inhibitory cytokine IL-10 themselves, inducing secretion of IL-10 from nearby cells, or by direct cell-to-cell contact. Some evidence exists that Treg function is impaired in patients with allergic diseases [12]. In fact, the concept of subcutaneous immunotherapy (SCIT) and sublingual immunotherapy treatment (SLIT) is centered on inducing Tregs through high dose allergen extracts [15]. In addition to activating Tregs, immunotherapy also functions by increasing IgG/IgE ratio, inhibiting initial activation of inflammatory cells, and shifting the Th2 to a Th1 response [16]. Other allergy treatment modalities such as antihistamines, decongestants, and steroids only act on a component of the allergic inflammatory cascade and only treat symptoms, not the root cause.

Pathophysiology of Migraine

The brain tissue itself does not contain nociceptive fibers and therefore cannot sense pain. Dural nerves that innervate cranial vessels do however have nociceptive function and are the main players involved in producing symptoms associated with

migraines [17–19]. A plexus of largely unmyelinated C fibers and thinly myelinated Aϑ fibers arising from the ophthalmic division of the trigeminal ganglion surround pial, arachnoid, and dural blood vessels as well as large cerebral and venous sinuses [20, 21]. Activation of these nociceptors by mechanical, electrical, or chemical stimulation has produced migraine-type pain, throbbing headaches with associated nausea, photophobia, and phonophobia [20]. These trigeminal fibers contain substance P and calcitonin gene-related peptide (CGRP) that are released when the trigeminal ganglion is stimulated, leading to increased extracerebral blood flow [22]. In an acute migraine, CGRP is elevated and normalizes with treatment. Studies have demonstrated that stimulation of cranial vessels induces pain [17, 19]. In vitro, triptans have been shown to act on the CGRP promoter and consequently regulate CGRP secretion from neurons; however, triptans can only have this effect once the trigeminovascular system is activated and the appropriate receptors are exposed [23]. These triptan receptors are located within the central nervous system, found at every level of sensory input from trigeminal ganglion through the cervical, thoracic, lumbar, and sacral dorsal root ganglia [24].

Historically, vasodilation of intracranial vessels was thought to be the underlying pathophysiology of migraine; however, recent studies have demonstrated that activation of a specific neuronal pathway induces the symptoms of migraine. Amin et al. [25] found no evidence of extracranial vasodilation in patients undergoing spontaneous migraine. Studies on migraine treatment medications are particularly supportive of the neuronal rather than the vascular theory. Serotonin receptor agonists were initially developed as cranial vasoconstrictors, but pure neural acting 5-HT receptor agonist, lasmiditan, is effective at aborting migraines and causes no vasoconstriction. Newer CGRP drug receptor antagonists (olcegepant, telcagepant) are effective at aborting migraine and also have no vasoconstrictive properties. Additionally, vasodilating substances such as vasoactive intestinal polypeptide (VIP) have been tested for their ability to induce a migraine with no migraine triggered after administration [26]. Migraine pain is caused by specific receptor site activation that starts a chain reaction of neural events rather than vasodilation itself, which is merely a byproduct of the neural cascade. Overall, migraine headache depends on both activation of the trigeminovascular pathway via transmission of pain signals originating in peripheral intracranial nociceptors and on inherent dysfunction of CNS structures involved in modulation of neuronal excitability and pain [20].

Sensitization occurs in migraine sufferers as demonstrated by the symptoms of photophobia and phonophobia. Approximately two thirds of patients experience allodynia, which is pain from non-noxious stimuli. Sensitization likely has a central and peripheral component [27]. The central component likely involves sensitization of thalamic neurons whereas the peripheral component functions via release of local inflammatory markers to activate trigeminal nociceptors [28, 29].

Genetic Basis of Allergic Rhinitis

Predominant genetic mutations in allergic rhinitis sufferers are found in genes encoding the a-chain of the high affinity receptor for IgE (FceRa1), RAD50, located adjacent to the gene for interleukin-13 (IL-13), and signal transducer and activator of transcription 6 (STAT6), which is regulated by IL-4 and IL-13. Genome wide association studies have substantiated that T-helper 2 cytokine genes are involved [12]. Essentially, allergic rhinitis sufferers have increased sensitivity to IgE and a predisposition for a more active Th2 mediated response.

Genetic Basis of Migraine

Numerous genetic mutations have been found in migraine with aura sufferers with most mutations effecting ion channels. A mutation now known as FHMI involving calcium channel gene CACNA1A is responsible for about 50% of migraine sufferers in identified FHM families and mutations in the ATP1A2 gene that codes for Na/K ATPase for about 20%; both mutations result in modulations in glutamate transport [18]. These known mutations suggest the pathophysiology of migraines is a result of ionopathies. Despite the genetic predisposition, environmental factors including stress, exposure to irritants, temperature fluctuations, and other triggers affect severity of the condition [30].

Epidemiology and Disease Burden

Headaches are among the leading causes for outpatient office and emergency room visits annually. Migraine may be episodic or chronic in nature. Most patients presenting to otolaryngologists for sinus headaches suffer from chronic, daily headaches and a subset of these patients suffer from chronic migraines. Headache must be present on more than 15 days per month for at least three months to be quantified as a chronic headache disorder. Approximately 5% of the domestic population suffers from chronic daily headaches, and of these, chronic migraines is by far the most frequent and debilitating. Episodic migraine affects up to 12% of the global population, whereas around 2% of the general population has chronic migraine disorder. Furthermore, the proper diagnosis of chronic migraine is often elusive, as only 20% of patients who fulfill the criteria are actually or ultimately diagnosed [2, 31]. Considering roughly one out of every seven Americans meet the diagnostic criteria for migraines, our low diagnostic rate certainly warrants improvement.

The total annual cost of chronic migraine, which includes diagnostic tests, outpatient or emergency room visits, and treatment interventions, is over three times

that of episodic migraines. Chronic migraine has a total annual cost of approximately $8200 per individual, whereas episodic migraine costs around $2600, with the majority of these direct medical costs attributable to pharmaceutical utilization [32]. Considering these costs for the U.S. population alone coupled with the high prevalence of migraines domestically, the indirect healthcare expenditures are quite staggering.

Similarly, allergic rhinitis is one of the most common health conditions worldwide. In the U.S. alone, over 60 million people carry the diagnosis of allergic rhinitis with at least $5 billion in direct healthcare expenditures [2, 33–35]. Expenditures as a result of allergies on a whole are far greater and approach $15 billion [36]. Allergic rhinitis is the most common chronic health condition domestically in the pediatric population and is expected to continue to rise. Comparatively, hay fever was estimated to affect only 1% of the U.S. population in the 1940s [36]. Allergic rhinitis has a significant impact on quality of life and absenteeism as well. It accounts for several million lost school and work days annually and affects around one in six Americans, with lost productivity approaching $1 billion [2, 36]. The impact has reached a global scale as well and in Europe, projections estimate that 50% of their general population will be affected by allergies within the next 10 years [37].

Surprisingly and despite the significant disease burden of allergic rhinitis, only a small percentage of patients actually seek formal treatment for their condition. A National Medical Expenditure Survey found that only 12.4% of patients with allergic rhinitis visited physician offices for management, whereas the majority of patients used over-the-counter or home remedies [36]. Notwithstanding treatment, approximately 50% of allergic rhinitis sufferers report their symptoms last more than four months per year, and about 20% of patients have symptoms for nine months or longer, which attests to the degree of impairment in quality of life.

Clinical Associations

Given the high prevalence of both migraine and allergic rhinitis, it is not surprising that the conditions are often seen in conjunction. Certainly, inflammatory sinus or nasal disorders can worsen or even precipitate headaches, but there is not necessarily a direct causal relationship. The disorders may share similar symptoms and clinical features, such as nasal congestion, rhinorrhea, periorbital or retro-orbital pressure/pain, facial discomfort or a sense of fullness, dysosmia, and lacrimation. The presence of autonomic symptoms is a primary characteristic of migraines. Barbani et al. [38] found that nearly 46% of patients with migraines had autonomic symptoms, including rhinorrhea, nasal congestion, lacrimation, and conjunctival injection. Another study of 100 patients with chronic migraines demonstrated the most frequent autonomic symptoms as lacrimation in 49%, conjunctival injection in 44%, eyelid edema in 39%, aural fullness in 30%, and nasal congestion in 20% [39]. A host of other data has shown autonomic symptoms as a concomitant clinical

feature in migraines [2, 38–42]. While an exhaustive explanation of migraine criteria is beyond the scope of this chapter, it is interesting to note that despite abundant literature highlighting autonomic symptoms in migraines, these features are not included in the current diagnostic criteria. Furthermore and contrary to much mainstream belief, migraines do not typically present with an aura. In fact, migraines without aura are far more common in chronic headache patients. The classic aura is seen in about 20–25% of patients with migraine. The absence of an aura further confounds the clinical picture and may lead to diagnostic errors.

Migraine and allergic rhinitis also share certain seasonal and environmental triggers. The exposure to topical or inhaled chemical and environmental irritants, barometric pressure changes, and seasonal variations may exacerbate symptoms of both migraine and allergic rhinitis. Several studies have shown that migraine and allergic rhinitis are both worse in the spring, summer, and fall months as a result of allergic triggers [43–46]. Due to comorbid allergic rhinitis, migraine patients seek more treatment during the allergy months as their headache intensity and ocular complaints worsen during this time period and almost 15% of migraineurs report seasonal exacerbations [43]. In a Turkish study of 80 AR patients, migraine headaches were detected in 50% of cases, compared to 18.75% in the non-AR, control group. Only 5% of AR patients with migraine had associated auras, and these results were statistically significant [47]. As part of a Norwegian Health Study, over 51,000 patients completed headache respiratory disease questionnaires. Headache disorders were found to be 1.5 times more likely in patients with asthma, allergies, and chronic bronchitis [9, 48].

Although there are some variations, multiple studies have shown that migraines are far more common in the AR population and the broader umbrella of headaches is more frequent in atopic disorders as a whole [2, 10, 47, 49]. Certain foods have also been cited as migraine triggers. Food elimination diets, namely chocolate, milk, and caffeine have shown dramatic reductions in migraines for certain patients [10, 50]. Food allergens have also been postulated as a link to migraine disorders. Mansfield et al. found almost a 70% improvement in migraines following dietary restrictions in a subset of patients with skin test positive food allergies [10, 51]. However, it is well established that non-allergic mechanisms also play a role as certain chemical irritants and preservatives, such as ethanol, sodium nitrate, phenylethylamine, tyramine, benzoic acid, and monosodium glutamate have all been implicated in food-related migraines [10, 51].

Martin, et al. [52, 53], have explored the relationship between atopic disease and migraine. They found that 32.5% of 536 consecutive allergic patients were diagnosed with migraine as well, but the prevalence of migraine was not altered by an increasing degree of allergic sensitization. The study did find some statistically significant frequencies of migraine in smaller subsets of patients upon finely massaging the data, but their clinical relevance is uncertain [52]. In a survey of episodic migraine sufferers, 17% had asthma and were twice as likely as their non-asthmatic cohort to progress on to chronic migraine one year later. In fact, the severity of asthma correlated with a greater likelihood of the progression [53]. One cannot infer causality from these epidemiologic data sets, but these studies are

intriguing. The pathophysiology of these disorders are unique, but some overlap and even potential common pathways are evident in the immune response, inflammatory modulators, and the role of pain receptors on symptoms and clinical features. Certainly, further research into pathophysiologic mechanisms is needed to elucidate the complex interplay between migraine and allergic rhinitis.

Conclusion

Migraine and allergic rhinitis are extremely common conditions with a significant healthcare and socioeconomic burden. Both conditions have a high prevalence and when they coexist in the same individual, the result can be very debilitating with a profound impact on quality of life. Allergic rhinitis is an immune-mediated process primarily involving the peripheral nervous system whereas migraine is a neuronal ionopathy primarily involving the central nervous system. Both processes involve sensitization of trigeminal nociceptors and the neurotransmitters substance P and CGRP, but downstream effects and symptomatology differ. While some pathophysiologic mechanisms and components may overlap, further research is needed to explore the relationship between migraines and allergic rhinitis. Similar characteristics and a high rate of comorbidity between these disorders can make a definitive diagnosis quite challenging; therefore, an astute level of suspicion together with a thorough clinical history and physical exam can help elucidate the diagnosis. An enhanced degree of global clinical awareness of the relationship, similarities, and differences between migraines and allergic rhinitis can help direct therapy, reduce direct and indirect healthcare expenditures, and improve patient morbidity and overall quality of life.

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Chapter 8
Vestibular Migraine

Michael Thomas Teixido and Mohammad Seyyedi

Introduction

While the association between migraine headaches and vestibular symptoms has long been noted in the literature [1–5], the term "vestibular migraine" was first used by Boenheim [6] in 1917 and recently reused by Dieterich and Brandt [3] in 1999. Vestibular migraine is the current nomenclature used by International Headache Society (IHS) to define vestibular symptoms associated with migraine headache. It was in 2013 that for the first time the International Headache Society [7] and the Bárány Society defined the criteria for the diagnosis of vestibular migraine as a distinct diagnostic entity. Vestibular migraine (VM) is also referred to in the literature as migrainous vertigo, migraine associated vertigo, definite migrainous vertigo, and probable migrainous vertigo.

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Diagnostic criteria for VM were initially described by Neuhauser et al. [5] in 2001. The original definitions included definite and probable migrainous vertigo and focused on the co-occurrence of International Headache Society (IHS) criteria migraine and symptoms of vertigo. In patients considered to have definite migrainous vertigo, the headaches and vertigo occurred at the same time. Patients considered to have probable migrainous vertigo had vertigo symptoms that behaved like migraine—the episodes occurred in response to environmental, physiologic or food triggers typically associated with migraine, or merely responded to treatment with medications for prophylaxis of migraine. Using these criteria, a positive predictive value of 85% was found in a follow-up study conducted over 9 years. These definitions were accepted with some variation into the International Classification of Headache Disorders (ICHD) in 2013 where the accepted terminology is vestibular migraine.

Diagnostic Criteria for Vestibular Migraine

The diagnostic criteria described by the International Headache Society in collaboration with Bárány Society in the ICHD-3 beta version [7] describe vestibular migraine as:

A. At least five episodes fulfilling criteria C and D
B. A current or past history of migraine without aura or migraine with aura
C. Vestibular symptoms of moderate or severe intensity, lasting between 5 min and 72 h.
D. At least 50% of episodes are associated with at least one of the following three migrainous features:
    1. headache with at least two of the following four characteristics:
        (a) unilateral location
        (b) pulsating quality
        (c) moderate or severe intensity
        (d) aggravation by routine physical activity
    2. photophobia and phonophobia
    3. visual aura
E. Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder.

Simply stated, the above currently used criteria are vestibular symptoms that last 5 min to 72 h [7] which co-occur at least 50% of the time with classic migraine headache.

In the Bárány Society's Classification of VM, vestibular symptoms that qualify for a diagnosis of vestibular migraine include:

(a) Spontaneous vertigo:
    (i) Internal vertigo (a false sensation of self-motion);
    (ii) External vertigo (a false sensation that the visual surround is spinning or flowing);
(b) Positional vertigo, occurring after a change of head position;
(c) Visually induced vertigo, triggered by a complex or large moving visual stimulus;
(d) Head motion-induced vertigo, occurring during head motion;
(e) Head motion-induced dizziness with nausea (dizziness is characterized by sensation of disturbed spatial orientation).

Other forms of dizziness are currently not included in the classification of vestibular migraine. The criteria for VM have been intentionally created to be very restrictive to improve the quality of the epidemiologic and drug-efficacy studies in which they will be used.

Epidemiology of Vestibular Migraine

Neuhauser et al. [8] estimated that vestibular migraine has a lifetime prevalence of approximately 1% in the German population. The prevalence of HIS migraine in the US has been assessed at 13–18% and 25–33% of these individuals will experience vertigo along with their other migraine symptoms at some time [9–11]. This makes MV much more common than benign paroxysmal positional vertigo which has a lifetime prevalence [12] of 2.4%, Ménière's disease with a life time prevalence of 0.19% [13], and vestibular neuritis whose incidence is 3.5 per 100,000 [14].

Like migraine headache, vestibular migraine is 1.5–5 times more common in women than in men [1, 3, 5, 15]. While VM can occur at any age the most common patients are males and females in early mid-life for whom migraine prevalence is highest. These patients stand out in the clinic because they tend to be younger than most patients with senile BPPV, Ménière's disease, or senile multi-factorial dizziness. Epidemiological data have shown that migraine-related syndromes are the most common cause of vertigo and dizziness in children [16, 17].

Symptoms

As outlined in the criteria above, symptoms other than headache which are attributable to VM include spontaneous vertigo, positional vertigo, visually induced vertigo, head motion-induced vertigo, and head motion-induced dizziness with nausea [7]. The criteria exist as inclusion criteria to allow study of epidemiology

and drug efficacy in groups of patients whose clinical manifestations are so manifest that there can be little dispute about their inclusion. As is always the case in medicine, however, not all patients who will benefit from treatment in the trenches of clinical care will meet criteria established in the literature.

Forms of dizziness that are currently not included in the VM criteria but are experienced by patients include lightheadedness, heavy headedness, rocking, swimming sensations, rising or falling sensations, tingling sensation, distortions of spatial awareness, and excessive motion-sickness susceptibility [18]. Aside from patients with Mal de Debarquement syndrome who have a very particular history, the complaint of "rocking" can be attributed directly to central mechanisms. Whereas symptoms originating from a lesion in one labyrinth may result in a tonic deviation in one direction, the reversing rocking sensation is central and migrainous in origin in most cases. The rare exception to this rule is the rocking osscillopscia that can occur in rare patients with dura pulsing against an open labyrinth.

Patients often have extreme motion sensitivity, especially on back roads, escalators or elevators where visual-vestibular coordination is challenged. Head motion sensitivity is typical and is often severe enough to provoke a history suggestive of BPPV but that cannot be demonstrated on Dix–Hallpike testing.

In a study of a large German population, Neuhauser et al. reported that 67% of the participants with VM had spontaneous rotational vertigo, whereas 24% had positional vertigo [8]. Only 24% of the participants with vestibular migraine complained of headache concomitantly with vestibular symptoms. Head motion intolerance is a frequent complaint and has been reported by 31–77% of patients with vestibular migraine [1, 2].

The greatest numbers of VM patients who do not meet current criteria, however, are those who do not have headaches that meet criteria for migraine, migraine with aura or even VM as defined by the IHS. They typically relate a history of vestibular symptoms which started with concurrent typical or atypical headache symptoms such as generalized head or ear pressure, sinus pressure, or pressure or pain in the neck. These are all sites in the head and neck to which pain can be referred within the trigemino-cervical complex. Symptoms of headache often do not coincide at all with episodes of vertigo. Nonetheless patients with this history will respond to migraine treatment.

The majority of patients with VM do also have migraine headaches, however, these headaches may not be concurrent with the onset of their vestibular symptoms. Most patients think of their migraine headaches as an episode of occurrence within their lifetime rather than an inherited susceptibility they never lose, and which can manifest many different symptoms. Patients also do not understand that any migraine symptom may be triggered by the same triggers headaches are. A typical story, for example, is a patient with a past history of migraine who presents decades later with vestibular symptoms that are provoked by stress, weather change, and food triggers that used to provoke headache. Headaches are absent or present only as a vague head pressure.

Some patients have never had what they consider to be migraine headaches. Instead they have had sinus pressure, allergy headaches, frequent sinus infections, or head pressure.

Similar to migraineurs, patients can have a pattern of seasonal symptoms observed over years that is concurrent with allergy symptoms.

Other clues to the presence of migraine mechanisms presenting as vestibular symptoms are available to the careful historian. The ability to trigger even long-lasting symptoms of vertigo with a brief provocation is a common characteristic in VM. The duration of symptoms in VM is highly variable; symptoms can range from continuous for months at a time to momentary and occur many times per day. Overall, only 10–30% of patients with vestibular migraine fulfill VM diagnostic criteria [3, 5]. These patients respond to VM treatment.

In addition to different forms of dizziness, patients with VM may suffer from photophobia, phonophobia, osmophobia, visual, and other auras. These symptoms may support or help establish the diagnosis when formal criteria for vestibular migraine are not met [2, 18]. Auditory symptoms such as vague hearing disturbances, tinnitus, and aural pressure have been found in 38% of patients with vestibular migraine, but hearing is usually only mildly and transiently affected [19].

Diagnosis of Vestibular Migraine

The diagnosis of VM is clinical and relies heavily on a detailed history, but a careful neurotologic examination and formal vestibular evaluation can also be helpful. Vestibular testing has given insights into the ways VM may present in different individuals. Between attacks, the neurotologic exam and laboratory testing are generally normal but some abnormalities such as subtle saccadic pursuit dysfunction, persistent positional nystagmus, directional preponderance on rotational testing, and increased vestibular ocular reflex (VOR) time constant have been reported [1, 20, 21]. These findings tend to stand out because they occur in young individuals in whom central findings are not expected. Many patients cannot tolerate optokinetic stimulus or head shake even on a day they consider themselves asymptomatic, suggesting that, as in migraine headache, the brain remains sensitive to stimuli even between attacks. The most common finding seen on electronystagmography is nausea provoked by optokinetic testing and an inability to complete all 4 caloric irrigations because of excessive nausea.

During the acute vestibular migraine attacks, patients may present with spontaneous nystagmus, positional nystagmus or a combination of spontaneous and positional nystagmus [22]. Indeed, a unilateral reduction of peripheral vestibular function occurs in about 25% of patients and vestibulo-ocular asymmetry has been reported in about half of patients [23]. Inferior vestibular nerve dysfunction manifested as reduced cervical vestibular-evoked myogenic potential (cVEMP) testing has also been observed [24, 25]. These highly sensitive patients will often complain

they remained ill for many hours after the completion of testing; this triggerability of migraine mechanisms to strong stimuli is a hallmark of migraine disease.

It has been demonstrated that patients with VM have dramatically lower thresholds (greater sensitivity) to motion in certain planes than do both normal people and migraineurs without vertigo. This work may lead to the development of diagnostics specific to some mechanisms of VM [26–28].

Pathophysiology

Vestibular migraine refers to symptoms of dizziness and vertigo that can develop as a result of migraine mechanisms acting in different locations: at the cortex of the brain, in the brainstem, or in the labyrinth itself.

Cortex

In migraine, symptoms may be generated at the cortex from spreading depression over the area of the vestibular cortex [29, 30]. Vestibular symptoms generated in this way may occur in isolation or as an aura symptom of an associated headache, as much as visual scotoma may be experienced as an aura preceding a migraine headache [29, 30]. Symptoms created in this way are usually experienced as vertigo with a sense of self-motion and may be fleeting or last up to 20 min. Dizziness is considered a common aura symptom among patients experiencing migraine with aura.

Brainstem

The laterality of a migraine attack can be seen with functional imaging which will demonstrate increased metabolic activity in the trigemino-cervical complex on the side of the migraine episode. Functional imaging also demonstrates scattered areas of hyperactivity in the brainstems of migraineurs in highly variable patterns [31, 32]. Symptoms of vertigo may occur because of abnormal activity in the vestibular nuclei and vestibular pathways.

If the vestibular nuclei are affected, then symptoms of vertigo may occur because of derangements of processing of normal vestibular input. These changes may result in extreme sensitivity to head movement. Patients with symptoms generated in this way do not have an uncompensated labyrinthine lesion on clinical or laboratory examinations and generally do not respond to vestibular suppressant medications.

Inner Ear

Symptoms of vertigo may occur in patients with vestibular migraine because of direct effects on the inner ear. Direct injury to the labyrinth is possible in migraine as seen with caloric and cVEMP testing. The direct mechanism of this injury is unknown but likely relates to the innervation of the blood vessels of the inner ear by unmyelinated C fibers originating from the ophthalmic division of the trigeminal nerve (V1). These are the same C fibers, which innervate the cortical and dural blood vessels, and contain inflammatory neuropeptides which are released at the beginning of a migraine attack. The release of these neuropeptides causes inner ear plasma extravasation, blood flow changes, and abnormal firing of vestibular afferents, which are all potential mechanisms for symptom generation in VM [33–36].

Vestibular Migraine and Ménière's Disease

There is some speculation that Ménière's disease (MD) may be a complication of migraine in susceptible individuals. There is a relationship between MD, migraine, and VM. A co-occurrence of Ménière's and VM is often seen just as a co-occurrence of Ménière's disease and migraine headache is often seen. The prevalence of migraine in patients with Ménière's disease is 56%. This is much higher than the 13% prevalence of migraine in the general population.

It can be difficult to distinguish patients with endolymphatic hydrops from those with VM. Even with the presence of aural symptoms, it may be difficult since auditory symptoms like hearing disturbances, tinnitus, and aural pressure have also been found in 38% of VM patients [1, 19]. The inner ear and intracranial blood vessels share the same innervation. So, the neuropeptides known to be important in the generation of migraine symptoms may play a role in the Ménière's disease pathophysiology and it is not surprising that Ménière's disease and VM share their response to similar food triggers, stress, weather changes, and allergy. Patients with bilateral aural symptoms that fluctuate in unison are manifesting disease in the central nervous system that affects both labyrinths and will respond to migraine management.

Treatment of Vestibular Migraine [37]

The treatment of VM is the same as the treatment of migraine headache, and takes its guidance from the frequency, duration, and severity of symptoms. In migraine management a decision must be made about the strategy of treatment: will it be abortive at the time of attacks, preventive to prevent attacks, or will both strategies

be necessary? In VM abortive medications work poorly compared to agents available for treatment of head pain. In addition, vestibular suppressant medications help only 20% of VM patients. Therefore, a strategy of migraine prevention is preferred in VM.

For most patients preventive treatment involves the reduction of migraine triggers such as trigger foods through diet modification as well as the elevation of threshold for triggering of migraine with preventive migraine medication. Environmental, physiologic, and dietary triggers may add up on a particular day to push a patient over their personal migraine threshold. Migraine symptoms, whether vestibular or headache related, may occur whenever the threshold is exceeded (Fig. 8.1). Reducing trigger loads commonly results in less frequent and less severe breakthrough symptoms.

Food Triggers in Migraine

There is a common misconception that if a person is sensitive to a food item they will know it. This is not true except for the strongest triggers. Many food triggers may not be potent enough to cause migraine alone, but may increase an individual's migraine threshold modestly for days. In combination with other partial triggers, a patient may be pushed over their personal migraine threshold and experience episodic or continuous symptoms. Patients with VM should therefore be encouraged to

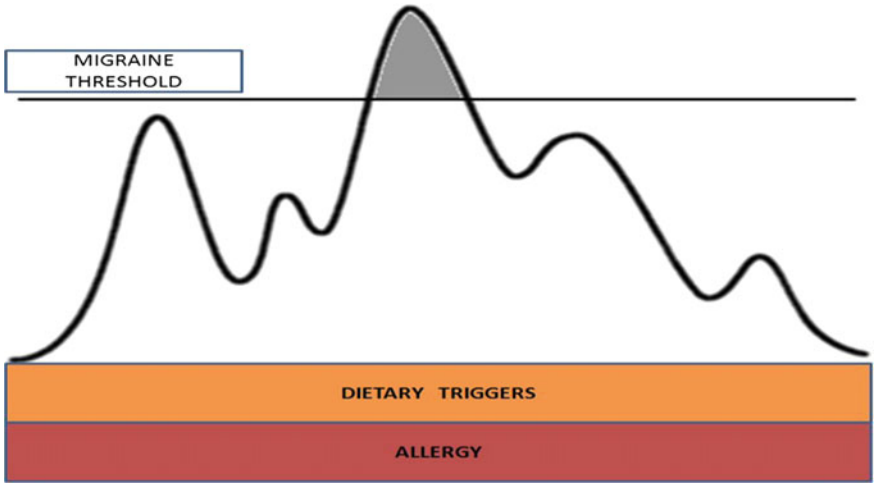

Fig. 8.1 Everybody is born with a threshold for migraine headache. Some have lower threshold due to inherited ion channelopathies. Crossing the threshold results in headache, dizziness, or other migraine symptoms. One way to treat these patients is to elevate the threshold with preventive medications and to decrease known migraine triggers. In this way the threshold is not exceeded and symptoms will not occur

reduce known migraine food triggers in their diet. Many patients can control symptoms in this way and avoid prophylaxis with anti-migraine medications. There is a **14%** treatment success in VM with caffeine cessation alone [38].

Food triggers of migraine fall into two general groups (Table 8.1) [39]:

- Foods that contain complex products of food aging and fermentation: wines, aged cheeses, fresh baked bread, yogurt, etc.
- Foods that contain chemicals that are potent CNS neurostimulants: caffeine, chocolate, tyramine in aged cheese, MSG, etc.

Table 8.1 Dietary migraine triggers [39]: patients should eliminate foods on this list or reduce their consumption to once weekly

Accent seasoning	Fresh bread	Pizza dough
Aged meats	Frozen yogurt	Plant protein
Anchovies		Processed meats
Autolyzed yeast	Garbanzo beans	Protein concentrates
Avocados	Gelatin	Protein fortified items
	Glutamic acid	Provolone
Bacon	Grapefruits and juice	
Bagels	Gravy	Raisins
Bananas	Gruyere cheese	Raspberries
Beef jerky		Ready-to-eat meals
Blue cheese	Hams	Red plums
Bouillons	Heavy alcohol drinks	Red vinegar
Breadcrumbs	Hot dogs	Red wine
Brewers yeast	Hydrolyzed protein	Restaurant food
Brick cheese		Rice protein
Brie cheese	Iced tea	Romano cheese
Broad Italian beans		Roquefort cheese
Broth	Kombu (seaweed extract)	
Buttermilk		Saccharin
	Lemons and juice	Salami
Calcium caseinate	Lima beans	Salty snacks
Camembert cheese	Limes and juice	Sauerkraut
Canned meats	Lentils	Sausage
Carrageenan	Liverwurst	Seasoned salt
Caviar	Low calorie foods	Smoked fish
Champagne	Low fat foods	Smoked meats
Cheap buffets	Lunchmeats	Snow peas
Cheddar cheese		Sodium caseinate
Cheese spread	Malt extract	Soft pretzels
Chicken livers	Malted barley	Soups

(continued)

Table 8.1 (continued)

Chinese food	Maltodextrin	Sour cream
Chocolate	Marinated meats	Soy products
Clementines	Mozzarella cheese	Soy protein
Coffee	MSG	Soy protein concentrate
Coffee cake	Muenster cheese	Soy protein isolate
Coffee substitutes		Soy sauce
Cola	Natural flavors	Stilton cheese
Croutons	Navy beans	Sulfites
Cultured items	Nitrates	Sweet n' Low
Cured meats	Nitrites	
	Nut butters	Tea
Dark alcohol drinks	Nutrisweet	Tenderized meats
Dates	Nuts	Textured protein
Decaf coffee		Tyramine
Decaf tea	Olives	
Doughnuts	Onions	Ultra-pasteurized items
Dried fruits with sulfites	Oranges and juice	
	Papayas	Vegetable protein
Enzyme modified items	Parmesan cheese	Veggie burgers
	Passion fruit	
Fava beans	Pate	Whey protein
Fermented items	Pea pods	Wild game
Fermented meats	Pepperoni	
Feta cheese	Pickled fish	Yeast
Figs	Pickles	Yeast extract
Flavored snacks	Pineapples and juice	Yogurt
Flavorings	Pinto beans	
Fresh beef liver	Pizza	

Some common foods such as peanuts and banana have unknown causes of chemical provocation of migraine. The use of a patient handout with dietary recommendations is recommended. Patients with frequent symptoms are encouraged to reduce food triggers on the list to only once per week. This allows them the freedom to function socially while reducing their dietary trigger load substantially.

The first goal of dietary trigger reduction is to achieve intermittent rather than daily symptoms. When a week passes and a MV episode occurs, the patient can look back over the previous 36 h and consider what may have triggered their attack; was it environmental, physiologic or dietary? Typically, a common pattern will emerge for each patient that points out their strongest triggers, those they should continue to avoid, and they can add other foods back with careful observation.

Sometimes the patient's strongest triggers are not dietary and lifestyle management to avoid stress, fatigue, dehydration, or hunger are employed to avoid symptoms.

Medication Treatment of Vestibular Migraine

Abortive treatment is rarely helpful in the treatment of VM because symptoms do not respond to treatment or are too brief or frequent for abortive medications to be useful.

Some patients with VM respond to centrally acting promethazine during acute episodes better than meclizine or diazepam. This suggests a central mechanism of action and origin of symptoms. Overall only 20% of patients with VM respond to peripheral vestibular suppressants during vertigo episodes. Medication treatment, therefore, must necessarily focus on elevation of the migraine threshold to prevent recurrent attacks.

Preventive Medications for Vestibular Migraine

Preventive medications are highly effective and useful in individuals whose symptoms are frequent or severe enough to warrant daily preventive medication. Medications useful for preventive therapy include tricyclic antidepressants, β-blockers, sodium channel blockers, calcium channel blockers, and long acting benzodiazepines.

Migraine is thought to be an inherited disorder of defective ion channels in the brain; therefore, many preventive drug therapies are ion channel antagonists. The best choice of an initial medication is best determined by the patient's current medications for other medical problems, their general health, and their willingness to accept side effects.

Patients are encouraged to start on medications early, and to tolerate side effects if they are mild, and to continue diet modification so that their symptoms can be interrupted, preventing chronification that may lead to resistance to treatment. After symptoms have been controlled for several months a weaning of medication to determine the smallest effective dose is reasonable.

The drugs below are presented by class in the order of their preference.

Tricyclic Antidepressants

Nortriptyline and amitriptyline have the highest response rates in patients with VM. Despite a high side-effect profile, these drugs are typically very well tolerated since

they are effective at very low doses in VM. Nortriptyline is better tolerated than amitriptyline with similar efficacy especially in elderly patients. Nortriptyline is a medium potency sodium and calcium channel blocker, in addition to being a serotonin and norepinephrine reuptake inhibitor (SNRI).

An initial nightly dose of 20 mg is often helpful. Thirty percent of patients at this dose will have some symptoms of slow waking in the mornings. These patients are instructed to take their medications earlier in the evening. If the patient has a definite but incomplete clinical response to the medication, the dose may be escalated in 10 mg increments to 30 then 40 or 50 mg. A few patients respond to higher doses of Nortriptyline. As expected, some patients have an excellent clinical response but have intolerable side effects. These patients should discontinue the medication and a trial of a sodium or calcium channel blocker can be started. Nortriptyline should be avoided in patients with bipolar disorder as it may exacerbate bipolar swings.

Patients can generally take low dose Nortriptyline successfully alongside other antidepressant medications but there is a small risk of serotonin syndrome. This should be discussed with the patient. At higher doses dry mouth and sedation can limit tolerance of therapy. Nortriptyline has a high response rate and good tolerance in older patients. Selective serotonin reuptake inhibitors (SSRIs) have less proven benefit in control of vestibular migraine and migraine headache.

Anticonvulsants

As a class, anticonvulsants are sodium channel blockers and have demonstrated a 25% response rate in VM patients. The most commonly used anticonvulsant is **topiramate**. It is a combination carbonic anhydrase inhibitor and sodium channel blocker. Treatment is started with 25 mg tablets and escalates by 25 mg weekly to an initial dose of 50 mg BID. Patients may require 100 mg BID. The most common side effects are associated with the carbonic anhydrase inhibitor properties and include taste disturbance (especially prominent with carbonated beverages), decreased appetite with moderate weight loss, and numbness and tingling of the extremities. Cognitive side effects of Topiramate can be limiting in up to 24% of patients but can be avoided in many patients with slow escalation as described. A 24-h release formulation of Topiramate has recently become available and has only a 4% incidence of cognitive side effects. Topiramate may be the best starting point for therapy in young female patients.

While its exact mechanism of action is unknown, gabapentin can be effective if the side effects of Topiramate are limiting. Patients are started at a low dose (300 mg a day) with weekly escalation to a first target dose of 300 mg TID. This can be increased as tolerated to 1200 mg TID or until side effects (usually sedation) appear. This agent has frequent dosing but a low side-effect profile.

Calcium Channel Blockers

Calcium channel blockers are the best-tolerated regimen for many patients. Verapamil 80 mg three times daily is often effective, and has the highest response rate but has a short half life requiring frequent dosing. Patients are instructed to taper their medication upward by taking 80 mg daily the first week, twice daily the second week then three times daily. Diltiazem CD 120 mg a day increasing as tolerated to as high as 240 mg twice daily is also effective. Constipation and hypotension are some times limiting side effects of calcium channel blockers. Avoid giving calcium channel blockers to patients already on beta-blocker therapy for hypertension. Patients should be cautioned about orthostasis which may limit utility.

Beta Blockers

Propranolol has long been used for migraine prophylaxis. Propranolol LA 60 mg per day may be increased as needed up to 160 mg per day. Propranolol should be avoided in patients with reactive airway disease, diabetes, and depression. Young men seem to have the highest response rate to beta blockers but limitations of exercise performance can be seen in athletes.

Benzodiazepines

Clonazepam at low doses is unusually effective in some patients who have symptoms of rocking at their presentation. One quarter to 1 mg twice daily can significantly reduce symptoms in these patients. This effect is seen even in patients who do not exhibit anxiety. Clonazepam can also be used in patients where stress is a major contributing factor to their illness. It should only be used as a bridge until life stressors are addressed with mental health professionals.

Allergy Treatment

Some patients with VM present a long history of symptoms with a distinctly seasonal pattern that suggests allergy as a triggering factor. It has been established there is a direct correlation between the degree of atopy and the intensity and frequency of migraine headache, as well as a headache response to treatment with allergy immunotherapy [40]. A treatment response among patients with VM has also been seen but has not been carefully studied.

Allergy testing for inhalant allergens and foods may be fruitful in establishing a connection of specific sensitivities to the patient's seasonal pattern. Testing may also detect unknown sensitivities to foods, which should be added to the list of

foods to be avoided. Routine treatment of allergy with antihistamines may be helpful.

Patient Follow-up

Effective treatment of VM requires significant time and counseling. Patients need to understand the migraine origins of their problem, and if they do not, to accept the rigors of a clinical trial in search of a solution to their problem. It is helpful to have materials prepared and easily accessible to them to completely enroll them into the work that is necessary to be successful. Many patients are understandably hesitant to take medications or modify their already healthy diets, or insist on natural treatments. It is important for patients to view their problem from the migraine paradigm to see the real health of their diet. Chronification of symptoms is seen in many patients who have experienced symptoms for years and may lead to resistance to treatment. For this reason, patients should be seen every 6–8 weeks to review changes in the frequency, intensity, and duration of symptoms of dizziness that have occurred in response to prescribed medications and adherence to the migraine diet. Reporting on headache symptoms in the same way is important because headache resolution is a marker of treatment response and may precede vertigo resolution. A partial response to treatment should lead to a recommendation of dose escalation if there are no limiting side effects.

Patients with concurrent Ménière's disease should have treatment directed at control of their hydrops. Surgical or chemical labyrinthectomy is avoided if headache or central symptoms of vertigo have not been controlled to avoid problems with post-labyrinthectomy compensation.

Many practitioners refer VM patients to their neurology colleagues. Most neurologists do not have a strong interest in seeing or managing these patients as they may not meet IHS criteria for the headache component of their symptoms, or even meet the ICHD vestibular migraine criteria. Neurologists typically see patients at 3–6 month follow-up intervals, which can lead to chronification of symptoms.

Summary

Migrainous vertigo is the most common disorder causing dizziness and vertigo among patients who seek care from otolaryngologists. Its mechanisms of actions have yet to be clearly understood but it responds to treatment using therapeutic strategies developed for the care of migraine headache sufferers. Symptoms of vertigo are varied and may originate in widely varying patterns among patients.

Migraine mechanisms can cause dizziness in patients because of dysfunction in the labyrinth, in the brainstem and at the cortex of the brain. A clear classification of VM has been adopted by the International Headache Society to allow high quality studies to improve patient care.

Recommendations

A care strategy for patients with vestibular migraine is now necessary in otolaryngologic practice. Because this plan necessarily involves migraine management, and because migraine is not currently a part of the otolaryngology curriculum, this chapter may serve as the starting point for creation of such a plan.

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Chapter 9
Migraine Comorbidities

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It is often a surprise to both migraine sufferers and medical professionals that migraine disease can affect other parts of the nervous system beyond the trigeminal nerve. The higher coexistence of migraine with other neurological diseases, cardiovascular disorders, and psychiatric illnesses underscores migraine heterogeneity [1].

This concept is easier to accept when a migraineur is reminded of the auras that cause painless zigzags across their vision at the onset of their headaches, or nausea and sound sensitivity that accompanies the headache, or the fatigue that follows a headache.

Some migraine-associated symptoms are described as auras, but, by definition, aura is a transient focal neurological disturbance, often associated with the onset of a headache. Auras appear gradually over several minutes and generally last less than 1 h. Symptoms can be visual, sensory, or motor. Examples of auras would be a tingling of the skin or sensitivity to sound during a migraine episode. While some auras are an early warning sign of an ensuing headache, other auras appear only during the headache phase, and finally some auras appear only after the headache has passed. An individual might have one or more auras. Other migraineurs have no auras. And still other sufferers have auras without a headache, such as an ocular migraine or osmophobia.

But what are we to make of other symptoms that are not associated with a headache and, unlike an ocular migraine, do not resolve within a short period of time but instead, last days, weeks, or months? For example, the person who complains of ear pressure or a sensation of a blocked ear has no dizziness to suggest

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Meniere's disease. Her tympanogram is normal and a myringotomy makes it feel worse. This is not likely to be eustachian tube dysfunction.

Although unproven, this person might be suffering from a sensory malfunction similar to allodynia. Allodynia, or the excess sensitivity of the skin, is a common dysfunction of the nervous system that is thought to be a side effect of chronic migraine where repeated acute episodes invoke neuroinflammation that is hypothesized to result in permanent changes to the central neural pathways—a phenomenon called central sensitization.

And there are conditions that appear to have the same underlying neural malfunctions as migraine headache sufferers but the symptoms do not involve a headache, such as cyclical vomiting syndrome. Other conditions appear to have a looser relationship with migraine headaches and are referred to as comorbidities. Examples would be mood disorders, tinnitus, or sleep disorders. It has been estimated that 83% of migraineurs have some form of comorbidity. Moreover, comorbidities contribute significantly to the headache-related disability [2].

There appear to be more than one form of migraine-related disorders. The common definition of comorbidity is the simultaneous presence of two disease conditions, but, since many migraine comorbid conditions do not present simultaneously with a headache, it is more appropriate to define comorbidity as the association of two diseases at a frequency greater than that expected statistically by chance. The significance is that, while many conditions share a history of migraine, they are not exclusively a form of migraine. Instead, a comorbid condition may relate to migraine in one of several different ways.

The relationship of migraine with several comorbid disorders is often identified on the strength of epidemiologic data or an effective response to migraine medication. The next step, which is currently not often known, is whether or not a comorbid condition shares a common pathophysiology with migraine disease.

The understanding of whether migraine disease relates to its comorbid conditions is complicated by the variable behavior of this disease within an individual. For example, some migraine-related pediatric conditions are transient and are considered precursors of migraine. The International Classification of Headache Disorders (ICHD-III beta) [3] has recently recognized childhood episodic syndromes as related to migraine. Pediatric comorbidities are associated with specific developmental stages. They include infantile colic (usually birth to one year of age), benign paroxysmal torticollis (1–5 years of age), benign paroxysmal vertigo of childhood (ages 3–9), cyclic vomiting syndrome (ages 5–12), and abdominal migraine (ages 8–18). Children with episodic syndromes have reversible attacks, but between attacks are otherwise healthy. They have strong similarities with migraine-prone children, regarding social and demographic factors, precipitating and relieving factors, and accompanying gastrointestinal, neurologic, and vasomotor features [4]. Children with episodic syndromes often have a positive family history for migraine and those with earlier-onset episodic syndromes may eventually develop migraine in adolescence or adult age [5]. The clinical improvement observed with migraine-specific drugs (triptans) further confirms the association of episodic syndromes with migraine.

Other childhood symptoms are not yet accepted as precursors of migraine. But conditions, such as paroxysmal tonic up gaze [6], recurrent abdominal pain [7], motion sickness [8], recurrent limb pain [9], and parasomnias [10] may emerge as having the same common etiology.

Although not exhaustive, Table 9.1 contains a list of symptoms, auras, diseases, or syndromes that have some association with migraine. This list is loosely organized by anatomic system. Otolaryngologists should become familiar with these conditions because they may be valuable in recognizing and treating both migraines and the migraine-related conditions.

How the medical community classifies the relationship between migraine and these comorbid conditions is in flux. The steady additions of clinical observations, epidemiologic data, therapeutic responses, and basic science findings continue to bring more clarity as to whether the relationships between these syndromes represent a true variation on the cellular defects of migraine disease or whether they should remain similar but essentially unrelated biological processes.

What follows is a brief synopsis of our current understanding of the relationships of migraine to many of its comorbidities. The first topic of vestibular migraine is a good example of how, over a few decades, our understanding of the effect of migraine pathophysiology on the vestibular nervous system has thoroughly changed our evaluation and treatment of balance disorders.

Central Nervous System

Balance

Vestibular Migraine

This condition is addressed in detail in another chapter but the story of vestibular migraine highlights the process by which a nonheadache condition is not initially recognized as having any relationship with migraine disease. Other explanations become entrenched in the medical body of knowledge. But clinical observations, followed by epidemiologic studies and now sophisticated imaging and vestibular testing is establishing this form of migraine as a leading cause of dizziness and balance disorders.

Although 30–50% of all patients with migraine describe occasional vertigo or dizziness associated with their migraine [11, 12], it was not until 1979 the first case series [13] reported benign recurrent vertigo of adults as a form of migraine. Other clinical observations of the association between balance disorders and migraine followed [14, 15].

These observations were followed by more convincing epidemiologic comparisons of vestibular symptoms in those with and without migraines. Epidemiological evidence shows that the comorbidity of vestibulopathies and migraine is three times

Table 9.1 Migraine comorbidities

Central nervous system
Balance
Vestibular migraine
Motion intolerance
Ataxia (Mal de Debarquement syndrome)
Benign paroxysmal vertigo of childhood/benign positional vertigo
Meniere's disease
Auditory
Hyperacusis
Tinnitus
Central processing disorder
Transient aphasia
Mood disorders (anxiety, depression, suicide)
Sleep disturbance
Restless leg syndrome
Glaucoma
Special sensory
Osmophobia
Phantosmia, phantageusia
Burning mouth syndrome
Sensory
Allodynia (including ear pain, pressure, foreign body sensation)
Red ear syndrome
Rhinosinusitis ("sinus headache")
Allergy
TMJ pain
Tooth pain
Trigeminal neuralgia
Thermoregulation
Autonomic dysfunction (Rhinosinusitis and gastrointestinal symptoms)
Red ear syndrome
Self-perception
Alice-in-wonderland syndrome
General cognitive disorders
Fatigue
Cognitive and memory deficits
Epilepsy
Concussion and traumatic brain injury
Musculoskeletal
Fibromyalgia

(continued)

Table 9.1 (continued)

Complex regional pain syndrome
Benign paroxysmal torticollis
Essential tremor
Idiopathic scoliosis
Cardiovascular
Stroke & heart attack
Hypertension/hypotension
Raynaud's phenomenon
Patent foramen ovale
Mitral valve prolapse
Functional gastrointestinal disorders
Irritable bowel syndrome
Cyclic vomiting syndrome
Gastroparesis and functional dyspepsia
Abdominal migraine
Colic
OB/GYN
Pregnancy complications
Pelvic floor pain
Interstitial cystitis, pelvic floor dysfunction
Vulvodynia

the prevalence by chance alone. Several balance syndromes occur more frequently in migraineurs than in controls, including benign paroxysmal positional vertigo, Meniere's disease, motion sickness, cerebellar disorders, and anxiety syndromes.

It is now more widely recognized that vestibular migraine (VM) is the most common cause for recurrent spontaneous vertigo with a lifetime prevalence in the general population of about 1% [16]. By 2016 VM was recognized as the most common cause of episodic vertigo in children and adolescents [17]. In one study of migraine headache sufferers with dizziness or vertigo, these concurrent symptoms were most common among menopausal women, where the average age of the subjects was 43.8 years and 89.5% were female [18].

VM is also distinctive for its wide range of symptoms (imbalance, spinning, ear pressure, tinnitus, visual impairment with photosensitivity, sound sensitivity, neck pain and spasms, confusion, spatial disorientation, and increased anxiety) [19] and variable duration (seconds to days) [20, 21]. The most recent version of International Classification of Headache Disorders (ICHD-III beta) recognizes VM as a subtype of migraine. The current ICHD-III beta criteria still does not account for the heterogeneity and natural history of the disorder [22].

An accurate assessment of VM prevalence is not yet possible due to the fact that many physicians struggle to identify VM in their patients [23]. In 2012 one vestibular clinic identified VM as 20.2% of the diagnoses, but only 1.8% of the referring doctors suspected this diagnosis [24]. This diagnostic challenge is highlighted by the diagnostic inconsistence between specialists. A survey reported that

neurologists diagnose a vestibular migraine in 82% of patients with vertigo and headache, while this opinion was shared only by 64.5% of otologists [25].

The diagnosis of VM lacks distinctive diagnostic criteria. Physical exam, blood test, and imaging are normal. The historical details of the vertiginous attacks, sometimes a spinning sensation and sometimes imbalance, with and without tinnitus and ear pressure, can overlap with the clinical presentations of Meniere's disease and benign positional vertigo [23]. The use of balance testing can help confirm a diagnosis but currently offer no pathognomonic findings.

The effectiveness of antimigrainous medications, both interventional (zolmitriptan) and preventive (nortriptyline, verapamil, metoprolol [21], propranolol and flunzarizine) [26] argues for the common pathophysiology of vestibular disorders and migraine [27, 28].

Nonetheless, the pathophysiology of VM is complex and unresolved. VM may share malfunctions with migraine in several mechanisms involving both the peripheral and central neural systems. In the inner ear serotonin receptors in the vestibular end organs as well as the trigeminal nerves are the same as found in migraineurs [29]. Calcitonin gene-related peptide (CGRP) and other neuropeptides, released during acute migraine attacks appear to affect both the peripheral and central vestibular systems [30]. PET scans have also revealed unique metabolic changes that may distinguish vestibular migraines as distinct migraine condition from other migraine syndromes [31]. And genetically-based ion-channelopathies may have peripheral and central dysfunctions [32]. Evidence from vestibular-evoked myogenic potentials (VEMP) testing of migraine patients has suggested that local inflammation of the anterior vestibular artery or vestibular nerve of the utricle is the cause of benign positional vertigo (BPV) in the absence of cupulolithiasis. The inflammation associated with migraine is the suspected culprit [33, 34]. VEMP promises to be a useful clinical tool to identify migraine versus Meniere's disease and BVP. Finally, the timing of spontaneous ataxia during menopause is likely to highlight the role of hormones in the pathophysiology of vestibular migraines.

Motion Intolerance

A history of childhood motion sickness has been found in 40–50% of pediatric and adult migraine sufferers, in contrast to less than 10% of controls [15, 35, 36]. It has been argued that motion sickness is a reliable minor criterion in the diagnosis of migraine in both children and adults [37].

And there is more intriguing evidence that a history of motion intolerance, particularly carsickness, might be a precursor of migraine and other comorbidities. One study found that childhood carsickness, allergies, and fatigue have correlated with migraine headaches during pregnancy [37]. And it has been hypothesized that childhood carsickness represents a propensity for chronic nociceptive sensitization in chronic migraine [38]. Perhaps future studies will strengthen the efficacy of a history of childhood motion intolerance to identify other adult migraine variants.

It should not be surprising that the proposed mechanisms of motion intolerance that link it to migraine are similar to those of vestibular migraine. Motion intolerance and migraine share similar interactions within the trigeminal system and vestibular nuclei [36], and, during a migraine attack, vestibular activity either sensitizes trigeminal nociceptive neurons or releases inhibitory controls on their discharge. Hyperexcitability of brainstem circuits produce symptoms of motion sickness and migraine, as well as heightened susceptibility to visual illusions of movement. Finally, vasomotor activity during a migraine attack causes vestibular dysfunction [39]. When Drummond found a lack of association between movement induced and visually induced motion sickness, he concluded that more than one mechanism increases susceptibility to motion sickness in migraine sufferers [39].

Mal de Debarquement Syndrome

Chronic rocking dizziness, often described as the feeling of being on a boat, triggered by prolonged exposure to passive motion, is known as Mal de Debarquement syndrome (MDS). Patients with motion-triggered MDS (MT) often develop new onset headaches. But the onset of MDS has been observed to occur without a motion trigger (non-MT). More than 40% of both groups developed migraine headaches. Though rocking dizziness does not meet current criteria for vestibular migraine, migraine physiology may predispose to, develop in, or worsen with the onset of chronic rocking dizziness [40].

Migraine, when combined with vertigo, may have more severe symptoms and worse prognosis. A survey of people with migraine headaches and vertigo had more headache, aura, nausea, vomiting, osmophobia, allergy, allodynia, headache increasing with head motion, noise as trigger for headache, days needing analgesics, and higher migraine disability scores than migraineurs without vertigo symptoms. This may reflect a difference in migraine pathophysiology [41].

Migrainous Positional Vertigo

In children, benign paroxysmal vertigo is characterized as sudden attacks of unexplained fright and imbalance. Vomiting and nystagmus are common. Autonomic signs such as dizziness, nausea, pallor, perspiration, photophobia, and phonophobia may accompany vertigo. The episodes last generally less than 5 min. The onset is between the age of 2–4 years and the frequency of attacks varies from once a day to once every 1–3 months [42]. Typically, children suffering from benign paroxysmal vertigo have a positive family history for migraine and a positive family and personal history for motion sickness. Some patients may develop other childhood episodic syndromes such as cyclic vomiting or recurrent abdominal pain [43].

In adults, benign recurrent vertigo (BRV) has been linked to migraine, including a familial form of BRV with features of migraine [44]. Report of a different clinical

response to benign positional vertigo and migrainous positional vertigo (MPV) reinforced the observation that there is another pathophysiologic explanation for some clinical forms of benign positional vertigo distinct from cupulolithiasis [45].

The etiology of these forms of vertigo is still speculative, including recurring vascular effects on the inner ear [46] to more neurogenic cause [47].

Meniere's Disease

Prosper Meniere was the first to suggest a possible link between Meniere's disease and migraine. The frequent occurrence of migrainous symptoms during Ménière attacks suggests a pathophysiologic link between the two diseases. People with Meniere's disease have over 50% lifetime prevalence of migraine compared to 25% of controls [48].

Auditory

Hyperacusis (Phonophobia)

Individuals with *hyperacusis* find sounds of low intensity uncomfortable. In neurology *phonophobia* is used specifically for the noise intolerance reported by patients with migraine [49]. Hyperacusis, the more widely used term for sound sensitivity, is intended to include all of the etiologies of this condition. Although the two existing epidemiological studies are small, the estimated prevalence of hyperacusis is between 8 and 15.2% [50, 51].

Hyperacusis is to be distinguished from *loudness recruitment*. This condition is associated with sounds of moderate intensity being perceived as louder than normal and is related to cochlear hearing loss and dysfunction of the outer hair cells of the organ of Corti. Loudness recruitment does not vary with mood [52].

Similarities between phonophobia and photophobia [53], as well as hyperacusis and tinnitus [51], have led to speculation of common pathophysiological mechanisms.

Tinnitus

While epidemiological data on the prevalence of tinnitus among migraine sufferers is scarce, one large study found the incidence of tinnitus among young adults with headaches was 8.9% [53]. A coexistence of hyperacusis and tinnitus has been observed. Hyperacusis can be a coincidental complaint of 40% of people with tinnitus [54–56]. 86% of people with hyperacusis also report tinnitus [57]. While hyperacusis, tinnitus, and migraine have several potential pathophysiological

mechanisms [58], it appears that they share common ground [59], such as possible neuronal hypersensitivity in the brainstem. The practical application of this hypothesis is that desensitization therapy appears to be helpful for both tinnitus and hyperacusis [52]. Tinnitus sufferers have high rates of depression due to insomnia and problems with concentration and emotion [60]. Stress reduction decreased tinnitus and depression and affected neural connectivity changes in the brain [61]. And anecdotally, trigger point injections and occipital nerve blocks have resolved tinnitus during a migraine attack [62].

Central Processing Disorder

There are several articles that point to migraine as contributing to impaired central auditory processing in both children [63] and adults [64, 65].

Transient Aphasia

Transient aphasia is a symptom rarely associated with migraine, but it can be considered as an aura when abnormal brain activity affects Wernicke's area where language and mathematics are processed. Fluent aphasia is when a person can speak but words and meaning are mixed up.

When a temporary neural dysfunction occurs more broadly in the occipital lobe, it can cause slurred speech and limb weakness. This phenomenon does not meet the diagnostic criteria for hemiplegic, ophthalmoplegic, retinal, or basilar migraines [66]. This form of aura can last an uncharacteristically long duration up to 24 h and therefore can be mimic a stroke.

Mood Disorders (Anxiety, Depression, Suicide)

Migraine headache have been strongly associated with depression and anxiety [67, 68]. One large epidemiologic report found the incidence of depression in migraine patients more than three times controls and the risk of anxiety and migraine comorbidity five times controls [69]. Those with depression appear to have more than twice the likelihood of suffering from migraine [70].

The relationship of migraine and depression has some unique elements. First, there is a bidirectional relationship in risk. Major depression increased the risk for migraine, and migraine increased the risk for major depression. Migraineurs have a more than three-fold risk of developing depression compared with nonmigraine patients, while depression patients that have never suffered from migraine have a more than three-fold risk of developing migraine compared with nondepressed patients [67].

Secondly, there is evidence that depression precedes the evolution of episodic into chronic migraine and that there may be a causal relationship [71]. Middle-aged women with migraine or nonmigraine headache are at increased risk of incident depression [72]. Frequent migraine attacks (weekly or daily) were associated with the highest risk for developing depression. Chronic migraineurs are twice likely to have depression than episodic migraineurs [72, 73]. Psychiatric comorbidity indeed affects migraine evolution, may lead to chronic substance use, and may change treatment strategies, eventually modifying the outcome of this important disorder. This comorbidity with psychiatric disorders has also been described for chronic tension-type headache and for chronic daily headache [74].

The prevalence of anxiety among migraineurs is not irrefutably established. One study identified the occurrence of anxiety in a migraineur at about 20%, in contrast to 15% of the general public [75]. Yet a large epidemiological survey found anxiety was present in migraineurs at 3 times more frequently than controls [76]. And about 5% of migraineurs suffer from both depression and anxiety, and 5.1% of both, higher than the 3.8% of the general population [74].

Chronic failures with serotonin receptors in the brainstem may explain the common pathophysiology between migraine and mood disorders [77, 78]. But it is likely that there is a more complex relationship between these conditions. The increased coexistence of mood disorders and chronic headache disorders raises the likelihood that their common pathophysiology is related to progressive changes in the pain and mood-controlling pathways in the subcortical brain. This evolving comorbid state between migraine and mood disorders may be similar to the process by which migraineurs develop allodynia via chronic sensitization. The higher prevalence of migraine and anxiety disorders with balance disorders in adults [29] and children [79] further points to a complex interaction of brainstem nuclei and networks.

Knowing that someone has depression and/or anxiety can be a red flag for migraine. Also, awareness of a patient's history of depression or anxiety can influence the choice of preventive medications. Those with depression might tolerate amitriptyline while propranolol and other beta-blockers might exacerbate their depression. Depression, anxiety, and migraine are all common and understanding the common elements of their disease mechanisms will help in improving the diagnosis and treatment of all three disabling disorders.

Patients with migraine and depression have a three times increased risk of suicide attempts [80]. It is recommended that all people with migraine be screened for depression, but special attention should be given to migraineurs who are young, unmarried, or physically limited [81]. Other groups at risk of suicide, *independent of depression*, are young adolescents with a history of migraine with aura and high headache frequency [82] and pregnant women [83].

Sleep Disturbance

Sleep disturbance is a common complaint among patients with migraine. Insomnia is the most common sleep disorder among migraineurs but may also include obstructive sleep apnea, periodic limb movement disorder, circadian rhythm disorder, and hypersomnia. Sleep disorders and headaches occur in men, nonpregnant women, and children. The risks of sleep disorders among migraineurs is also higher among pregnant, particularly overweight, women [84]. One study reported 83.7% of females with chronic migraine awoke feeling tired [85].

Sleep disturbances can precipitate headaches, particularly morning headaches and chronic headaches [86, 87]. Over one third of migraineurs reports difficulty initiating and maintaining a normal sleep pattern. And almost 40% of those who slept less than 6 h per night were more likely to suffer more frequent and more severe headaches [86].

Epidemiological studies indicate that sleep deprivation is one of the most common precipitating factors for migraine attacks. Depression and anxiety are comorbid with both headache and sleep disorders (especially insomnia). Management of sleep disorders may improve or resolve headaches, as well as psychological comorbidities [88].

There are hypotheses that sleep disorders and migraine may share abnormal synthesis or secretion of melatonin, for headaches [89] and chronic headaches [90], as well as serotonin [87]. Serotonin secreted from the dorsal raphe nuclei is implicated in both the control of sleep cycles and migraine pathogenesis [91, 92]. The hypothalamus is likely to play an important role in controlling sleep and pain, because the suprachiasmatic nucleus of the hypothalamus regulates the release of serotonin. Central nervous system generators regulate sleep and medical conditions, such as obstructive sleep apnea and depression, may disrupt sleep and lead to nocturnal and morning headaches [93]. Insomnia may represent an independent risk factor for headache chronification. The identification of sleep disorders, alone or in association with depression or anxiety, may be useful in episodic headache patients to prevent chronification [94].

Restless Legs Syndrome

Restless Legs Syndrome (RLS) is a condition characterized by uncomfortable and sometimes painful sensory disturbances in the lower limbs producing an irresistible urge to move in order to relieve the sensation. Lifetime prevalence of RLS among migraineurs is approximately 11% [95] and the incidence of RLS in migraineurs increases with age. Most of people with RLS had migraine without aura. The frequency of RLS in migraineurs is more than three times the frequency in those without a migraine history [96].

This migraine-RLS comorbidity extends to additional increased illness risks. First, RLS increases with increasing number of migrainous symptoms [95]. Secondly, approximately 50% of headache patients with RLS have sleep disturbances [97]. Thirdly, there is an association between migraine, RLS and depression [96].

Family histories of migraine and RLS support a genetic underpinning of this disease association [98]. Migraine and RLS may have a joint origin, based in part on a common genetic linkage mapped to chromosome 14q21 [99]. Similar to sleep disturbances, dopaminergic imbalance could be the pathogenic connection between migraine and RLS [96, 98]. While dopamine agonists are effective therapy for RLS, it is not yet known if control of RLS will reduce other migraine symptoms.

Glaucoma

Headaches were present in 86% of elderly low-tension glaucoma patients (70 year of age or older) but in only 64% of elderly normal subjects and only 59% of elderly ocular hypertensive patients. Because migraine is an ischemic disorder, its possible association with low-tension glaucoma has etiologic and therapeutic implications [100].

Special Sensory: Olfaction

Osmophobia

Migraine patients often report osmophobia, an oversensitivity and intolerance to smell. Approximately 40% of adult [101] and 35% of pediatric migraine sufferers [102] reported osmophobia during an attack. The least well tolerated smells were scents, food, and cigarette smoke [101]. The absence of this symptom among people with tension-type headaches appears to make this a complaint a clinical indicator of migraine [101, 102].

Phantosmia & Phantageusia

Phantosmia, the perception of a specific, unpleasant smell, usually a burning sensation, occurs in less than 1% of headache sufferers. The typical hallucination lasts 5–60 min, occurs shortly before or simultaneous with the onset of head pain. In the majority of patients, phantosmias diminishes or disappears with initiation of prophylactic therapy for headaches [103]. Unlike visual, sensory, language, brainstem, and motor symptoms, the International Classification of Headache Disorders currently does not recognize phantosmia as a form of aura.

While the pathophysiology of this condition is unknown, one study indicates that decreased GABA levels in the brain mark this event. This finding, along with similarity of sensory hallucinations with epileptic seizures and migraines, suggests that there may be common biochemical changes among these two disorders [104].

Recent studies reinforce that the reduced blood flow associated with this migraine aura is secondary to neuronal dysfunction rather than primary cerebrovascular ischemia [105] (Phantageusia, the perception of tastes that are not actually present, appears to have a similar pathophysiology [104]).

Burning Mouth Syndrome

Primary burning mouth syndrome (BMS) is a chronic intraoral pain condition for which no local or systemic cause can be found and clinical examination is normal. BMS is characterized by a continuous burning sensation of the oral mucosa, typically involving the tongue. This hallucination mostly affects elderly citizens, especially postmenopausal women with prevalences up to 12 and 18%. People can also suffer from taste alterations (dysgeusia) [106, 107]. The pathophysiology is complicated with several neuropathic mechanisms at different levels of the nervous system. Low GABA levels are implicated and this biochemical phenomenon is common among epileptic seizures and migraine [104].

Sensory

Allodynia

Cutaneous allodynia, the perception of pain induced by a nonpainful stimulus (touching the skin, brushing hair, or cleaning an ear canal) is frequently associated with migraine, especially when chronic, and mainly in the aura subtype. 60–79% of migraineurs report this symptom [110, 108, 109] Allodynia is more frequent during a headache attack (acute allodynia) than in-between attacks (interictal allodynia). Acute allodynia is generally referred to the painful region but may diffuse to other areas of the head and, even other parts of the body [110].

Allodynia can be associated with other comorbid pain conditions (irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia) and psychiatric conditions (depression, anxiety) [111].

Allodynia is a common manifestation of central nervous system sensitization in migraine patients. The pathophysiology of acute allodynia involves a transient increase in the responsiveness of central pain neurons that process information from skin and intracranial structures. It also involves irritation of meningeal perivascular pain fibers [108]. With repeated inflammation secondary to acute attacks may alter

the regulation of the central nociceptive pathways. Lowering the neuronal pain threshold induces central sensitization in the caudal nucleus of the trigeminal nerve. In contrast, extracephalic allodynia is likely mediated by thalamic sensitization [110].

Chronic migraine sufferers often complain of persistent minor but annoying symptoms, such as blocked ears, water in the ear, or a foreign body in the deep ear canal. These symptoms are often dismissed because people assume that this is just some eustachian tube dysfunction, residual water from bathing or a hair irritating the eardrum. But careful examination, combined with normal tympanography and myringotomy, can undermine these easy explanations. Instead, particularly when patients also seem to be excessively sensitive to the touch of their ear canal skin or have a history of migraine disease, it is more plausible that these are hallucinations involving spontaneous activation of the middle and outer ear sensory systems in the same way that some forms of allodynia occur chronically and without any relationship to headaches. These symptoms may be another form of chronic central sensitization.

Red Ear Syndrome

Red ear syndrome (RES) is a rare disorder of unknown etiology, pathophysiology, or treatment that was originally described in 1994. The defining symptom of RES is redness of one or both external ears, accompanied by a burning pain. The prevalence and incidence of RES is unknown. The median age of onset of RES is 44 years old, although a wide range of 4–92 years is reported. The duration of each episode can vary widely. The majority had attacks lasting 30–60 min. However, a few people have reported short attacks lasting seconds and others report a constant ear pain.

The attack frequency varies immensely both among sufferers and within individual sufferers. The majority of RES patients report daily attacks, ranging from one to 20 attacks a day [112].

A common pathophysiology between RES and migraine is suspected because of the clinical similarities and occasional coexistence. While the precise mechanism is not known, there are several possible etiologies. Both conditions may share dysregulation of brainstem trigemino-autonomic circuits [113]. As it is the sympathetic dysregulation, not a parasympathetic activation, that is the predominant mechanism for the ear reddening, it seems less likely that the trigemino-autonomic reflex plays a central role at least in isolated cases of RES.

There is a plausible argument for the antidromic discharge of impulses along C3 leading to the release of vasodilator peptides and subsequent pain and vasodilatation [114]. It resembles backfiring C-nociceptors syndrome where temperature changes alter the mechanical trigger threshold [115].

Allergy

Sixty-five percent of patients with migraine reported also having allergic rhinitis, according to one study of 6000 patients with migraines. This study suggests that allergic rhinitis is the most common comorbid illness. In contrast, the comorbid frequency of depression or anxiety is about 25%. People with migraine and allergies were 33% more likely to have frequent migraines than people who had no allergies. The research shows not only that rhinitis is common in those with migraine headache, but also that migraine patients with allergic and nonallergic rhinitis triggers have more frequent and disabling headaches [116].

In another epidemiological study of 294 patients, 34% allergic rhinitis patients had migraine headaches while only 4% of the patients without allergic rhinitis had migraines. In other words, if one has allergic rhinitis there is a 14 times higher risk of migraine headaches [117].

In a larger survey of 3831 individuals with active rhinitis (AR) symptoms versus nonsufferers, AR patients suffer from several comorbid conditions, including sinusitis (31 vs. 7%), migraine (17.3 vs. 8.3%), and depression (17.2 vs. 8.3%). AR patients also reported high rates of fatigue, sleep problems, and reduced concentration [118].

Rhinitis is essentially an exaggerated response to stimuli because neural activity is upregulated as a result of a pathologic process, primarily inflamation. All symptoms of rhinitis can trigger through neural pathways. This phenomenon is known as neural hyperresponsiveness. Neural function can be chronically upregulated in the presence of mucosal inflammation, acutely with an allergic reaction or even in the absence of inflammation as in cases of nonallergic rhinitis. The sensory nerves of the nose arise from the trigeminal nerve and consist of myelinated and unmyelinated fibers. Unmyelinated fibers are slow conducting and belong to the nociceptor, C-fiber type. Unlike the sharp pain of myelinated fibers, the unmyelinated fibers produce a more prolonged dull pain or pressure. These fibers are connected through the trigeminal ganglion to the subnucleus caudalis and subnucleus interpolaris, which are involved in pain modulation. C-fibers are unusual because they can release inflammatory neuropeptides (substance P and neurokinin A) and calcitonin gene-related peptide peripherally and thereby produce vasodilation and increased vascular permeability, also known as neurogenic inflammation [119]. Through granules transported within the cytoplasm of C-fibers, these neuropeptides can contribute to central sensitization.

While not fully understood if allergies trigger headaches or if migraineurs have symptoms that mimic allergies, one of the theories is that the inflammatory substances, particularly histamine, released from the mast cells and basophils during an allergy attack activate the trigeminal afferents that richly innervate the nasal cavities and paranasal sinuses, making headaches more frequent and severe. Secondary release of nitric oxide in the paranasal sinuses may play a role in pain generation [120].

Treatment of allergic rhinitis with nasal steroids, antihistamines, or allergy shots may improve any headache symptoms that accompany them. Immunotherapy reduced the frequency and disability of migraine headaches in younger patients [121].

Rhinosinusitis ("Sinus Headache")

Currently the concept that migraine may be the cause of patient's complaints of acute, recurring, and chronic rhinosinusitis is not widely accepted. The location of pain and pressure over the cheeks, eyes and forehead, combined with a runny nose and nasal congestion convinces patients that they are suffering from a "sinus" infection. The most common features associated with sinus headache include nasal congestion (56%), eyelid edema (37%), rhinorrhea (25%), conjunctival injection (22%), lacrimation (19%), and ptosis (3%) [122]. Unfortunately, these are the same symptoms that are described in established criteria for the diagnosis of acute or chronic rhinosinusitis [123]. The distinguishing features of purulence in acute rhinosinusitis and documented sinus mucosal inflammation are often overlooked in diagnosing and treating patients.

There are several epidemiological studies that point out that the majority of these patients have symptomatic criteria to meet the diagnosis of a migraine condition. Among 58 patients with a diagnosis of "sinus headache" made by a primary care physician and without mucopurulent discharge, 95% met the criteria for a headache disorder [124]. A study of 130 migraine patients with a past history of sinusitis, only 24 (18.5%) had convincing evidence of sinusitis [125].

Other clinical studies reveal that patients presenting with rhinosinusitis respond poorly to medical treatment of sinusitis [126], do not have imaging consistent with sinus infection or inflammation [127–129], do not improve with sinus surgery [125], and do improve more dramatically with therapy directed at migraine [130].

An estimated prevalence of migraine disease in people with rhinosinusitis symptomatology is 30–88% [124–128, 130, 131].

The concept of migraine chronification is central to understanding this atypical presentation of migraine. An understanding of migraine disease as a congenital but evolving dysfunction of the trigeminal nerves that innervate the paranasal sinuses provides a plausible explanation of how a hypersensitive trigeminal innervation of the paranasal sinuses could replicate the central facial pressure and pain associated with a sinus infection. The explanation of neurogenic inflammation and chronic sensitization are explained in the section of allergy. These phenomena are applicable to the mucosa and C-fibers of the paranasal sinuses. Mucosal inflammation from infection or allergy could stimulate the dull chronic pain and pressure of C-fibers. Or, alternatively, these trigeminal nerves can initiate the sinus mucosal swelling and a secretory response that are mistaken for a sinus infection.

A secondary dysautonomia of the superior salivatory nucleus explains how a neuropathy of the central nervous system, particularly the brainstem, might cause turbinate swelling and excessive nasal secretions, conjunctival erythema and

lacrimation that mimic the nasal congestion and rhinorrhea and, sometimes, the ocular symptoms of rhinosinusitis. Parasympathetic innervation of the nasal airways and ethmoid sinuses originate from the facial nucleus of the brain stem and the superior salivatory nucleus. Their fibers innervate serous and mucous glands, arteries, veins, and arteriovenous anastomoses [132]. The release of neurotransmitters (acetylcholine), neuropeptides (vasoactive intestinal peptide (VIP) and others) causes glandular discharge, vasodilatation, and sinusoidal engorgement. Nitric oxide (NO) synthase, which is responsible for NO production, is also released from the trigeminal nerves in the nasal and sinus cavities [119].

The challenging aspect of this diagnosis is that this form of headache does not meet any specific headache diagnosis, according to current International Classification of Headache Disorders (ICHD) criteria.

TMJ Pain

Temporomandibular disorder (TMD) symptoms are more common in migraine, episodic tension-type headaches, and chronic daily headache, relative to individuals without headache. The strongest association is with migraine [133]. Individuals with myofascial TMD had a higher prevalence of self-reported migraine and chronic fatigue syndrome than those with nonmyofascial TMD [134]. The pathophysiologic mechanism of trigeminal nerve hypersensitivity associated with migraine could explain this presentation as TMD [135].

Tooth Pain

There are many cause of orofacial pain, but atypical odontalgia has been defined as an acute severe dental pain with no recognizable odontogenic cause and is reported to be prevalent in 2.1% of orofacial pain. One way to think of idiopathic dental pain is as a presentation of trigeminal neuropathy [136]. But, since trigeminal neuralgia is simply another form of orofacial pain involving the trigeminal nerve, migraine has the potential to mimic other types of pains, such as toothache or sinusitis [135].

Trigeminal Neuralgia

Trigeminal neuralgia (TN) is a chronic pain condition that affects the trigeminal nerve. Even mild stimulation of the face may trigger a jolt of excruciating pain. TN is a rare disease, estimated between 0.01 and 0.3%, but it might be higher. The gender ratio of women to men is approximately 2:1. TN can first appear at any age, but disease onset occurs after the age of 40 years in more than 90% of cases, and the peak age of onset is between the ages of 50 and 60 years. This demographic pattern roughly duplicates that of migraine. The revised International Classification of Headache Disorders-3 (ICHD-3) suggest three TN variants: (1) classical trigeminal

neuralgia, often caused by microvascular compression at the trigeminal root entry to the brainstem; (2) trigeminal neuralgia with concomitant persistent facial pain; and (3) symptomatic trigeminal neuralgia, caused by a structural lesion other than vascular compression.

The current opinion is that the proximal compression of the trigeminal nerve root close to the brainstem by a tortuous blood vessel (an artery or vein) leads to mechanically twisted nerve fibers and secondary demyelination, probably mediated by microvascular ischemic damages. These changes lower the excitability threshold of affected fibers and promote cross talk between adjacent fibers. Thus, tactile signals coming from the fast myelinated (A-beta) fibers can directly activate the slow nociceptive (A-delta) fibers, and sometimes C-fibers, resulting in the high-frequency discharges characteristic of TN. Symptomatic TN can result from tumors (either benign or malignant), multiple sclerosis, or arteriovenous malformations [137].

Migraine is a newly identified risk factor for the development of trigeminal neuralgia. This argument is based on data showing a high epidemiologic risk of migraineurs to develop TN. The common hypersensitization of the trigeminal nerve suggests that there could be a common pathophysiology [138]. The female prevalence and the emergence of TN during the perimenopausal period raise questions about the role of estrogen depletion on this condition.

Thermoregulation

At the end of the list of symptoms accompanying an acute migraine headache is fever. This symptom is estimated to occur in 9% of pediatric migraine attacks. It is known that cytokines are releases in the wake of a cortical spreading depression and the release of inflammatory agents in migraine may have a secondary effect on the thermoregulatory center in the hypothalamus. But the prevailing theory is that serotonin and possibly other neurotransmitters regulate thermic homeostasis and therefore when this system is malfunctioning as part of the migraine condition, it can interfere with a person's internal thermostat [139].

Autonomic Dysfunction

Epidemiological data on trigeminal unilateral autonomic symptoms in patients with migraine are scarce, but in 2007 Obermann [140] reported one out of four migraine patients regularly experiences one or more unilateral autonomic symptoms during their attack. Elsheikh reported 78 patients with nonallergic, noninfectious rhinitis, termed dysautonomia rhinitis, had more than one regional and multisystem complaint in addition to their nasal complaints. Dysautonomia is a multisystem disorder, including the vagal nerve. Beside the nasal symptoms, some otolaryngological

disorders may be explained on the basis of autonomic dysfunction [141]. Dysautonomia is the likely explanation for nasal congestion, rhinorrhea, conjunctival erythema and eyelid swelling, nausea, and vomiting associated with migraine. Malfunction of autonomic system is also a suspected cause of gastric stasis [142]. There are both episodic and chronic forms of autonomic dysfunction.

Self-perception (Alice-in-Wonderland Syndrome)

Alice-in-Wonderland syndrome, named for Lewis Carroll's principle character, is a disorder characterized by transient episodes of visual hallucinations and perceptual distortions, during which objects or body parts are perceived as altered in various ways. The common visual symptoms are micropsia (69%), teleopsia (50%), macropsia (25%), metamorphopsia (15%), and pelopsia (10%) [143]. The definitions are enlargement (macropsia) or reduction (micropsia) in the perceived size of a form and objects appear small and distant (teleopsia) or large and close (pelopsia) or a distortion of a perceived object (metamorphopsia).

This can be classified as a form of aura because it is a temporary change in self-perception. It is also been described in association of other childhood migraine variants such as abdominal colic [144] and visual "snow" [145]. This is one of several pediatric episodic migraine variants that are consistent with a multi-layered neurological disorder [146]. This condition has been linked to increased neural activity in the posterior parietal lobe and precuneus region of the brain where the brain's capacity for self-imagery is located. While the prevalence Alice-in-Wonderland syndrome is not known, it is relatively rare [147].

In a chart review of 48 patients (average age 8.1 years) with Alice-in-Wonderland symptoms, the etiology was infection (33%), migraine (6%), and head trauma (6%). No associated conditions were found in 52%. One quarter of patients without a history of migraine may subsequently develop migraine [143].

General Cognitive Disorders

Patients commonly complain that migraine affects their ability to think clearly. Neuropsychological exams, combined with imaging, showed that migraine could affect memory, attention, and speed of information processing [148]. Cortical dysfunction can occur both during migraine attacks and between them [149].

Fatigue

Fatigue includes feelings of tiredness, exhaustion, or lack of energy and is reported in 70–84% of migraine sufferers [150]. During an acute migraine attack, fatigue can

be a prodrome symptom, occur during a migraine attack, and linger after the headache has resolved.

Lack of energy between migraine attacks is cited as an important factor in reduction quality of life and productivity [151]. Migraine sufferers reported double the levels of exhaustion, compared to controls, during the first trimester of pregnancy. This was a stronger correlation in overweight migraineurs.

Chronic fatigue syndrome shares many of the same symptoms with migraine: depression, headaches, and sleep disturbance. There is suspicion that they share similar dysfunctions of the central nervous system.

Fatigue in patients with a chronic disease is divided into central and peripheral fatigue. Central fatigue results from abnormalities in neurotransmitter pathways within the central nervous system. Peripheral fatigue results from neuromuscular dysfunction outside the CNS and relates to impaired neurotransmission in peripheral nerves and/or defects in muscular contraction, due to energy depletion, inflammation, joint abnormalities, or muscle wasting [152].

The overlap with the pathophysiology of migraine is likely. Parallels have been drawn between the chronic fatigue syndrome and fibromyalgia [153, 154]. Dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis is suggested. Frequent symptoms in both chronic fatigue syndrome and fibromyalgia are pain, fatigue, sleep disorders, irritable bowel syndrome, chronic headaches, cognitive or memory impairment, dizziness, and impaired coordination. Issues of mental health concern, particularly anxiety and depression, often accompany each [154]. Additionally, fatigue ranks high among early symptoms of pregnancy and migraineurs had an increased risk of exhaustion [155].

Cognitive and Memory Deficits

Given the chronic changes to the central nervous system and increased risk of strokes, there has been speculation that migraine can lead to a general cognitive decline. Several cross-sectional studies have looked at the association between migraine and cognitive functioning, but the results of these studies have been mixed. In one long-term study the conclusion was that migraine does not affect cognitive decline [156]. Nonetheless, neuroimaging studies have identified frontal lobe brain abnormalities in migraineurs. Neuropsychological investigations highlighted frontal lobe related cognitive impairments in migraineurs, including working memory and executive function deficits. A study of gray matter density and psychological testing showed decreased frontal and parietal lobe GM density and slower response time in migraineurs, compared to control subjects. Delayed response time correlated significantly with reduced GM density of the frontal lobes in migraineurs. The conclusion was that migraineurs do have impairment in memory and executive function [157].

Epilepsy

Migraine and epilepsy share elements of clinical expression, pathophysiology, and treatment options. Both are episodic disorders that may be chronic and/or recurrent. Epidemiology demonstrates reciprocally increased incidences of epilepsy in migraineurs and of migraines in children with epilepsy [158]. Epileptic seizures and migraine headaches may be mistaken one for the other and may even overlap. In particular, occipital lobe seizures may be misdiagnosed as migraine auras [159]. Some have considered these two conditions as a continuum or spectrum and others have captured the spectrum with the term "migralepsy".

Basic and clinical neuroscience research findings suggest that cortical spreading depression (CSD) and epileptic foci may facilitate each other; furthermore, the threshold required for the onset of CSD has been suggested to be lower than that required for an epileptic focus. These data may explain the prevalence of epilepsy in migraine populations (ranging from 1 to 17%) and the frequency of migraine in epileptic populations (ranging from 8.4 to 20%) [160].

Migraine and epilepsy have common links at a cellular level involving synaptic glutamate release and similarities in the cortical spreading depression in migraine and the paroxysmal depolarizing shift in epilepsy. The study of a 22-year-old female migraineur with recurrent convulsive status epilepticus and ataxia revealed two genetic mutations. The conclusion was that these abnormal neuroelectrical conditions might be two forms of a mitochondrial disease [161].

Also, migraine and epilepsy share several pathophysiological mechanisms that involve neurotransmitters and ion-channel dysfunctions. Similar to the genetic mitochondriopathy of chronic epilepsy and ataxia, a hypothesis of a shared genetic susceptibility to migraine and epilepsy is strongly supported by genetic information from familial hemiplegic migraine [162].

Antiepileptic drugs, particularly topiramate, have been effective agents for prevention of chronic migraine and epilepsy, but the mechanism of action is still unclear [163].

Concussion and Traumatic Brain Injury

Concussion, which is defined as "a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces", is a poorly characterized clinical syndrome [164]. Repeated asymptomatic head injury has recently been recognized as a more serious and lasting brain trauma, involving both male and female athletes from an early age. Sports-related concussions are very common—8.9% of high school athletic injuries and 5.8% of collegiate athletic injuries, with an incidence of 0.23 per 1000 and 0.43 per 1000 athlete exposures, respectively [165].

Similar mechanisms are believed to be responsible for military service members who have sustained explosive blast-related traumatic brain injuries (TBIs).

Concussions can initiate a variety of symptoms, including loss of consciousness, amnesia, headache, blurred vision, dizziness, nausea, and attention deficit. At least 75% of all concussions are classified as mild, involving brief, if any, loss of consciousness and symptoms that are usually transient, with most patients recovering uneventfully. However, some patients have persistent or worsening cognitive, behavioral, or somatic symptoms, suggesting more profound, possibly progressive brain dysfunction. Posttraumatic headaches (PTHs) may persist to become chronic [166].

Headache is one of the most common symptoms after TBI and PTH and may be part of a constellation of symptoms that is seen in the postconcussive syndrome. Moderate to severe PTH that is often disabling may be classified as migraine or probable migraine and is found in substantial numbers of individuals. Recent data from civilian adult, pediatric, and military populations all find that PTH may be more of a chronic problem than previously thought, with a prevalence of close to half of the injured population. In addition, if PTH definitions are strictly adhered to, then many cases of PTH may be missed, thus underestimating the scope of the problem [167].

The relationship of TBI, PTH, and postconcussive syndrome with migraine is complex and not fully understood. Not only are the headaches of postconcussive syndrome mimicking those of migraine, but also there is some evidence to suggest that a personal history of migraine may be an independent risk factor for concussion [164, 167]. But whether a personal history of migraine is a risk factor for a worse posttraumatic neurologic outcome is unresolved. While one study revealed no clear evidence that premorbid headaches or migraine predict a prolonged postconcussion recovery [168], another study by the same researcher showed a statistically significant association between migraine symptoms and longer time to recovery [169]. Furthermore, two studies [170, 171] came to opposing conclusions about postconcussion neurocognitive deficits in athletes with and without migraine histories. Concussion may trigger migraine, migraine may be misdiagnosed as concussion, or they may coexist [172]. Mild head trauma can trigger both typical migraine and acute confusional migraine. Both are more prominent in male patients and are associated with a history of headaches, confusion, both family history and past personal history of migraine, and normal neuroradiological examinations [173].

In conclusion, there is some overlap in the pathophysiology of migraine and concussions, but current research has not clarified this relationship [174].

Distinct but difficult to clinically differentiate from concussions, there is an alternative diagnosis of trauma-triggered migraine (TTM). The exact epidemiology of TTM is unknown but has been described as early as the 1960s. The current diagnostic rate of TTM is most likely underrepresented, possibly due to the relative unfamiliarity with this disorder. TTMs occur most commonly in children and adolescents. Individuals who suffer from TTM typically have a family history of migraines and have a 70% chance of a parent or sibling having a history of migraines. Importantly, preventive treatment of migraines has been validated and proven effective. Therefore, TTM should be considered in the differential for recurrent trauma-induced headaches [175].

Currently the treatment of PTH may be acute or preventive. Comorbid conditions, such as migraine, should be considered when choosing an appropriate preventive therapy [167].

Of greatest importance is the overlap in the pathophysiology of brain trauma and acute migraine attacks. The immediate effects of TBI can include cell injury or death, neurovascular disruption, disturbances of ionic and neurotransmitter homeostasis, electrical, chemical, and energetic dysfunction. The initial inflammatory response to injury begins with activation of the innate immune system, production of an array of bioactive substances, alterations in the blood brain barrier (BBB), and involvement of the systemic immune system. Multiple cell types, including brain microvascular endothelia, glia, and peripheral immune cells, mediate these processes [166].

Glial cells, in particular, are key to the initiation and the pathological prolongation of neuroinflammation. Glial cells, the supportive cells that surround the central nervous system neurons, release cytotoxic proinflammatory substances, particularly cytokines (interleukin-1 (IL-1), especially IL-1β; tumor-necrosis factor alpha (TNFα); IL-6; and IL-10) that are intended to aid in the reparative process after injury. Unfortunately, in patients with chronic PTH, perpetuated microglial activity with continued release of cytotoxic substances, prolong the injuries and lead to the degeneration of neural pathways [176].

These cytokines are among the substances responsible for the evolution of acute trauma into a chronic pain syndrome, by increasing the permeability of the blood brain barrier and initiating and maintaining neuropathic pain. There are many other substances responsible for the evolution of acute trauma into a chronic pain syndrome. These include several inflammatory mediators. Matrix metalloproteinases (MMPs) are enzymes that mediate extracellular protein growth and breakdown. After injury, MMP synthesis increases to promote local repair but can concurrently degrade component proteins of the blood brain barrier. MMPs activate glia and thus can contribute to the development and maintenance of glia-mediated pathological pain after nerve injury. MMP levels (MMP-2 and MMP-9) have been shown to be elevated post-TBI, as well as in patients with migraine. Cortical spreading depression has been shown to upregulate MMP-9, with associated alterations in BBB permeability. Posttraumatic migraines share a number of pathological features between TBI and migraines [177], including evidence for an inflammatory component and glial involvement [178–180].

An explanation for the variability of PTH and understanding of what pathophysiologic conditions are risk factors for chronic headache will be important advances in curbing the evolution from acute brain trauma and recurring acute migraine attacks into chronic brain conditions. The similarities in the neuroinflammatory events that follow an acute migraine attack and acute brain trauma suggest that advances in understanding how to control this evolution from repair to despair would be applicable to treating both conditions.

Musculoskeletal

Fibromyalgia

Fibromyalgia (FM) is a condition that causes widespread pain, sleep problems, fatigue, and psychological distress. People with FM may also have other symptoms, such as morning stiffness, tingling or numbness in hands and feet, headaches (including migraines), irritable bowel syndrome, sleep disturbances, cognitive problems with thinking and memory, painful menstrual periods, and other pain syndromes.

The prevalence of this disorder increases with age from 2% at age 20 to as high as 8% at age 70. Prevalence was much higher among women than men (3.4 vs. 0.5%). That is a 7:1 female to male ratio [181]. These demographics resemble those of chronic migraine disease.

FM is more common among migraineurs than in the general population. Among chronic migraineurs, FM was present in 35.6%. Insomnia and depression predicted FM in patients with chronic migraine. Among general migraineurs, the prevalence of FM may be somewhere between 16% and 36% [182, 183]. And the reciprocal relationship is similar. Among FM sufferers, 76% had recurring headaches and 48% met migraine criteria [184]. Headache predated the onset of FM on average 7 years before represent a risk factor for fibromyalgia [185].

FM and migraine share other similar comorbidities. Between 40% and 70% of FM patients suffer from irritable bowel syndrome. FM patients have facial muscle pain, painful menstrual periods, cognitive or memory impairment, irritable bladder, and dizziness. Like migraine, FM symptoms worsen with changes in weather, cold or drafty environments, hormonal fluctuations (premenstrual and menopausal states), stress, depression, anxiety, and over-exertion.

These commonalities suggest that they have overlapping functional defects. First, both conditions share hypersensitivity to pain [186, 187] and, secondly, this abnormal pain processing is occurring, not in the peripheral, but in the central nervous system [188]. To further pinpoint the location of the central nervous system defects, functional MRI studies have confirmed that painful stimuli of both FM and migraine patients increases the activity of the anterior insula and cingulate cortex [189, 190]. Knowing that the musculoskeletal symptoms of FM are actually manifestations of abnormal neural function in the brainstem helps to explain the sleep disturbances, cognitive deficits, gastrointestinal malfunctions, and other symptoms of FM sufferers. At a cellular level both FM and migraine share defects in the serotonergic and adrenergic systems. Serotonergic medications help both FM and migraine patients by improving neural transmission in the central nervous system [191].

Complex Regional Pain Syndrome (CRPS)

Complex regional pain syndrome (CRPS) is a chronic pain condition most often affecting one of the limbs, usually after an injury or trauma to that limb. CRPS is believed to be caused by damage to, or malfunction of, the peripheral and central nervous systems. In contrast to fibromyalgia, it is usually constant, intense pain in only a single extremity and there is often localized swelling and skin color changes.

CRPS and fibromyalgia may share sympathetic nervous system dysfunction or a genetic mitochondrial disorder.

CRPS and migraine are chronic, often disabling pain syndromes. Recent studies suggest that headache is associated with the development of CRPS. One study found those with CRPS was 3.6 times more likely to have migraine. Migraine may be a risk factor for CRPS and the presence of migraine may be associated with a more severe form of CRPS [192].

Benign Paroxysmal Torticollis

Benign paroxysmal torticollis (BPT) is a rare dyskinesia of recurring episodes of abnormal head tilt or rotation, sometimes associated with vomiting and ataxia. During an episode it is possible to observe pallor, photophobia, ataxia, drowsiness, and headache, which resemble migraine features. The episodes often last from several hours to days, and have a spontaneous resolution. Typically, the frequency and duration of attacks decline as the child grows older with a definitive resolution at the age of 5 years. It appears most commonly between 2 and 8 months of age and resolves by age 3. Migraine may occur later in childhood.

Specific chromosomal mutations (CACNA1A, PRRT2) are associated with BPT as well as other paroxysmal disorders (paroxysmal kinesigenic dyskinesia, benign familial infantile epilepsy, choreoathetosis infantile convulsions, benign paroxysmal vertigo of infancy, abdominal migraine, cyclic vomiting, aura without migraine, and confusional migraine) [193, 194]. A genetic study identified a genetic mutation that has an age-specific manifestation as a defective neuronal calcium channel responsible for BPT [195].

Essential Tremor

The existence of an association between migraine and essential tremor has long been controversial. Many conditions may feature both headache and tremor, but rarely as core clinical symptoms at presentation [196]. But the findings from a case-control clinical study of 300 patients reported lifetime prevalence of migraine in essential tremor patients was significantly higher than that in controls (22.0 vs. 12.7%).

The dopamine receptor D3 Ser9Gly variant may be lower in essential tremor with migraine than the general essential tremor patients [197].

Idiopathic Scoliosis

Idiopathic scoliosis (IS) is defined as a lateral curvature of the spine greater than 10 degrees accompanied by vertebral rotation and affects 2–4% of adolescents. Idiopathic scoliosis can be further classified by age of onset: infantile (birth to two years), juvenile (three to nine years), and adolescent (10 years and older). Males and females are about equally likely to have minor scoliosis of approximately 10 degrees, but females are five to 10 times more likely to progress to more severe disease, possibly needing treatment [198]. Biomechanical, neurological, and postural abnormalities are some of the leading causes of this affliction. One theory argues that impaired sensory input and/or impaired motor output within the brain causes maturational delays that allow scoliosis curve progression to occur [199].

Cardiovascular

Stroke and Heart Attacks

Early epidemiologic studies identified migraines and other headaches, particularly those accompanied by aura, are associated with an increased occurrence of stroke/TIA symptoms and ischemic stroke events [200]. The worst of the damage is to the cerebellum [201]. A study of more than 100,000 US women, published in 2016, found that those who reported getting migraine headaches had a 50% higher risk of having or dying from a heart attack, stroke, or heart disease. Since only 1.2% of the women had a major cardiovascular disease event, the risk of this condition is only 1.8%, or 1 in 50. This study does not tell us about the risk of auras or whether the risk is equal among different racial groups. Questions remain about the mechanism and whether migraine treatment can also reduce the risk of heart attacks and strokes, but the use of aspirin as a preventive agent appeared to increase the risk of heart attacks [202].

Hypertension/Hypotension

A relationship between migraine and hypertension or hypotension is controversial. One study did report 5% incidence of diastolic hypotension during migraine attacks but it was not statistically significant [203]. But the effects of migraine on the

peripheral vascular system remain a question mark. For example, microvascular abnormalities in the retinas of middle-aged individuals with migraine and other headaches supports the hypothesis that neurovascular dysfunction may be related to the pathophysiology of headaches [204].

Raynaud's Phenomenon and Apical Ballooning Syndrome

The prevalence of Raynaud's phenomenon (RP) in migrainous patients was 26 versus 6% of controls [205]. In a study of patients with systemic lupus erythematosus and migraine, the prevalence of RP was 49.4% [206]. But the underlying common vascular pathophysiology is still unclear.

One study evaluated apical ballooning syndrome (ABS), migraine, and RP because they are characterized by female predominance, identifiable triggers, and, likely, vascular dysfunction. 44% of patients with ABS had a history of migraine versus 12% of controls. ABS appears to occur almost exclusively in postmenopausal women. A unique feature of ABS is the occurrence of a preceding emotionally or physically stressful event in approximately two thirds of patients. The precise incidence of ABS is unknown, but it may account for 1–2% of patients who present with an acute myocardial infarction.

While the association of ABS with migraine and RP supports a role of vasomotor dysfunction in the pathogenesis of ABS, it remains to be established whether impairment in microvascular function is the primary mechanism for the injury or is an epiphenomenon. The conclusion of one study [207] was that estrogen deficiency is not the primary factor in the pathophysiology. Another study [208] looked at the possible association of inherited prothrombotic risk factors in patients with primary RP and migraine, but concluded that the prevalence of other thrombosis-associated alleles did not differ between patients with or without migraine. The association of migraine and RP suggests that serotonin receptor agonists can be used with caution but avoided in patients with very severe Raynaud's syndrome [206].

Patent Foramen Ovale

Migraine has been associated with patent foramen ovale (PFO), a congenital hole in the heart, and PFO closure has resulted in partial or complete relief of migraine symptoms in several clinical studies [209–212]. Migraineurs with aura have a higher prevalence of PFO than migraineurs without aura and nonmigraineurs [209] and are about 4.5 times more likely to have >50% reduction in migraine frequency after PFO closure than migraineurs without aura [213]. Theoretical causal mechanisms include subclinical emboli or metabolites bypass the pulmonary circulation through the PFO and may be able to irritate the cerebral vasculature and trigger a

migraine or transient hypoxemia resulting from shunting of blood through the PFO causes microinfarcts in the brain [214].

Several other studies have not supported PFO closure for preventing migraine until more of this association is understood [215–217], including a randomized clinical trial of PFO closure for migraine [218]. Perhaps it is simply that PFO and migraine are inherited together but are physiologically independent [219].

Mitral Valve Prolapse

While heart abnormalities, such as patent foramen ovale (PFO), atrial septal aneurysm (ASA), and mitral valve prolapse (MVP) have been noted to appear more frequently in migraine sufferers, there is doubt that there is a clear connection between migraine and PFO, ASA, and MVP [220].

Functional Gastrointestinal Disorders

The central nervous system and enteric nervous system are linked by the vagus nerve. Not only does the brain send signals to the gut, but the communication is also bidirectional. Just as the brain can modulate gut functioning, the gut, and likely what we ingest, can influence our brain functioning. Additionally gut microbiota may also have effects on brain functioning and therefore this begins to explain how diet can affect migraine sufferers [221].

The association between migraine and functional gastrointestinal disorders has been confirmed by many clinical observations and epidemiological studies. Nausea, vomiting, abdominal pain, or diarrhea often characterizes migraine attacks. 78–88% of people suffering from migraine have migraine-associated nausea or vomiting [222, 223]. And approximately 80% of patients complaining of nausea or vomiting are likely to be migraineurs [224].

It is unknown why some subjects with migraine but few headache features have relatively prominent GI symptoms. It is speculated that differences in symptoms reflect the relative activity within the connected pain and solitary (nausea) nucleus in the brainstem [225]. Additionally it could be that periodic syndromes, such as colic, cyclic vomiting, and abdominal migraines are shifts in the balance between CNS nerve centers [224].

But functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), are reported in migraine patients between the attacks as well. 23–53% of IBS patients have frequent headaches. Migraine and IBS often coexist with fibromyalgia

and other chronic pain syndromes. Migraine and IBS affect approximately 10–20% of the general population, usually young adults. Both diseases are more prevalent in women [226].

Pathophysiologic explanations include the effects of hormones, neuroimmunology, stress, and hyperactivity of the hypothalamic-pituitary-adrenal axis. The enteric nervous system as a source of numerous neurotransmitters and visceral reflexes is a plausible common pathogenic link between IBS and migraine. In particular, serotonin, the main neurotransmitter of the gastrointestinal tract, plays a relevant role in the pathogenesis of IBS as well as migraine [226]. Agonists and antagonist of serotoninergic receptors are the most efficacious drugs for IBS, functional dyspepsia, and migraine. Tricyclic antidepressants reduce sensations in response to food, including nausea, and delay gastric emptying, especially in females. Buspirone appears efficacious in functional dyspepsia; amitriptyline was not efficacious in a large trial of children with functional gastrointestinal disorders [227].

Cyclic Vomiting Syndrome

Cyclic Vomiting Syndrome (CVS) is characterized by recurring, self-limited episodes of severe nausea and vomiting, separated by weeks or months. In children there is a prodromal phase, lasting about 1.5 h, characterized by worsening nausea and a dramatic autonomic dysfunction (decreased muscle tone, pallor, lethargy, and apathy). Intense vomiting, accompanied by persistent nausea, anorexia, retching, increased salivation, abdominal pain, headache, pallor, photophobia, and phonophobia, follows. This phase lasts an average of 24 h [228].

Although it can occur at any age, the most common age at presentation is 3–7 years. There is no gender predominance. The precise pathophysiology of CVS is not known but a strong association with migraine headaches indicates that it may represent a mitochondriopathy. Studies have also suggested the role of an underlying autonomic neuropathy involving the sympathetic nervous system in its pathogenesis [229]. Cyclic vomiting syndrome is also believed to be a brain-gut disorder involving neuroendocrine pathways in genetically predisposed individuals [230, 231].

Therapeutic recommendations include lifestyle changes, prophylactic therapy (e.g., cyproheptadine in children 5 years or younger and amitriptyline for those older than 5), and acute therapy (e.g., triptans) No mortality has been reported as a direct result of CVS and many children outgrow it over time. A subset may develop other functional disorders like irritable bowel syndrome and migraine headaches [232].

Gastroparesis and Functional Dyspepsia

Gastroparesis (*GP*) is a chronic disease of either the muscles of the stomach or the nerves controlling the muscles that causes delayed emptying of solids and liquids without evidence of mechanical obstruction. Patient with gastroparesis have a range of uncomfortable feelings after eating, including unusual fullness, nausea, loss of appetite, heartburn, regurgitation of food or acid, and belching. *Functional dyspepsia* (*FD*) is defined as a difficulty digesting food and has the same presenting symptoms. Importantly, however, delayed gastric emptying is present in 30% of patients with FD.

GP and FD are the two most common sensorimotor disorders of the upper gastrointestinal tract. The prevalence of FD is estimated at 10%, and that of GP is approximately 1.5–3% [233, 234]. Researchers and clinicians classify these disorders into separate and distinct categories. However, this classification system confuses both patients and clinicians, as symptoms are similar and treatment is frequently the same. Instead of categorizing these two neuromuscular disorders as completely distinct disorders, it may be more appropriate to view them as a broad, continuous spectrum [235].

The etiology of FD includes a genetic predisposition, viral infection, stress, inflammation, surgery, trauma, or Helicobacter pylori infection, and hormonal influences. Similarly, the etiology of GP is multifactorial, including diabetes, prior surgery, ischemia, connective tissue disorders, radiation, inflammation, medications, and vaccinations. The common ground with migraine is the observation that FD and GP are related to dysfunctional neurotransmitters (nitric oxide), neuropeptides (e.g., CGRP), and enteric nervous system function [236–238]. Certainly migraine attacks are characterized by a period of gastric stasis, similar to idiopathic gastroparesis [239]. Patients with migraine and those with gastric stasis exhibit abnormal autonomic nervous system function [240]. Patients with the primary complaint of epigastric pain are also treated with medications that overlap with migraine therapy (e.g., tricyclic antidepressants, tramadol, gabapentin, duloxetine) [235].

The other relevant connection of these neuromuscular disorders with migraine is the effect of GP and FD on the delayed gastric absorption of migraine therapeutic medications [241].

Abdominal Migraine

An abdominal migraine (AM) is an idiopathic disorder, seen mainly in children, as recurrent attacks of moderate to severe midline abdominal pain, associated with vasomotor symptoms, nausea, and vomiting, lasting 2–72 h and with normality between episodes. Headache does not occur during these episodes. (3) (ICHD) AM

usually occurs in children who have a family history of migraines. AMs are rare in adults, but about 2% of all children may get AM.

Migraine management was most effective in relieving both prominent GI discomfort and headache [242]. A case report made the observation that the extracephalic symptoms of Idiopathic Stabbing Headache (abdominal and lower back pain) are likely linked to migraine [243]. Most children with AM will develop migraine headache later in life.

Colic

Infantile colic, which affects 5–19% of babies, may be a childhood episodic migraine syndrome. This conclusion was suggested by a three-fold higher reported incidence of colic among children and adolescents aged 6–18 years with migraine [244]. The pain and crying in some genetically predisposed infants could represent a form of *infantile migraine* with an age-specific expression. Earlier data suggested that children with migraine were more likely to have a personal history of infantile colic and a family history of infantile colic or migraine in any of the first-degree relatives [245]. Data from 154 infant–mother pairs were analyzed. Infants with a maternal history of migraine were 2.6 times as likely to have colic as infants without a maternal history of migraine [246]. Unfortunately, research data is still limited and the certainty of migraine as the underlying etiology is still unconfirmed [247].

OB/GYN

Pregnancy Complications

Women with a history of migraine disease are at increased risk of hypertension [248], preeclampsia [249], premature birth [250], and placental abruption [251]. The association of migraine with endothelial dysfunction and vascular disease may be the explanation of these interrelated complications of pregnancy [249].

Interstitial Cystitis, Pelvic Floor Pain, and Dysfunction

Interstitial cystitis (IC), also known as painful bladder syndrome (PBS), bladder pain syndrome (BPS), and chronic pelvic pain, is a chronic inflammatory condition

of the submucosal and muscular layers of the bladder. It usually consists of recurring pressure or discomfort in the bladder and pelvic region, sometimes with urinary frequency and urgency. Primary neurogenic inflammation (hypersensitivity or inflammation of pelvic nerves) is one of several potential triggers.

Many people with IC have problems with the group of muscles in the lower pelvic area and develop a condition called pelvic floor dysfunction (PFD). Like a sling or hammock, these muscles support the organs in the pelvis, including the bladder, uterus or prostate, and rectum. They also wrap around your urethra, rectum, and vagina (in women). In IC patients, PFD is usually related to the presence of too much tension (or high-tone), the opposite of the too-relaxed state (or low-tone) that contributes to incontinence. However, sometimes IC patients with PFD can have a combination of muscles that are too tense and too relaxed. The symptoms of PFD are painful intercourse and the need to bear down to urinate.

Migraine headache is common in women with chronic pelvic pain (67%), regardless of endometriosis, and contributes to disability in those with both conditions. Women with the most severe headaches had a lower quality of life compared with those with pelvic pain alone. The strong association suggests a common pathophysiology [252].

People with IC have comorbid central and autonomic nervous system disorders. Comorbid complaints include gastrointestinal symptoms suggestive of irritable bowel syndrome, dyspepsia, sleep abnormalities, severe chronic fatigue, fibromyalgia, syncope, and migraines. Patients with IC were found to have 16% comorbid anxiety, four times the occurrence in controls [253]. These comorbidities raise the possibilities that interstitial cystitis is part of a diffuse disorder of central, autonomic, and sensory processing affecting multiple organs outside the bladder [254]. A study of 8564 twins found evidence of shared genetic factors among several chronic pain syndromes, including chronic pelvic pain [255].

Vulvodynia

Vulvodynia is a chronic unexplained pain in the area around the vaginal opening. The symptoms, such as pain with first tampon insertion, vulvar burning, or burning with urination make prolonged sitting or sex uncomfortable. There is also a higher incidence of comorbid fibromyalgia among women with vulvodynia. Compared to women without vulvodynia, those with vulvodynia are two to three times more likely to have one or more other chronic comorbid pain conditions. Chronic pain conditions including vulvodynia, fibromyalgia, interstitial cystitis, temporomandibular pain, and irritable bowel syndrome are now known to be frequently underdiagnosed and are much more prevalent than previously estimated [256–260]. The Institute of Medicine reported that at least 116 million persons in the United States suffer from chronic pain, with national annual cost estimates of over $500 million [261].

Vulvodynia has several potential etiologies. Approximately one half of those with any one disorder met criteria for at least one additional condition. And the fact that some women present with multiple conditions and others report only one suggests differences in time of onset and differing subsets of pathophysiology [257]. A link of this condition to central neural pathology was tested and those with vulvodynia had greater activity than controls within the insula, dorsal midcingulate, posterior cingulate, and thalamus [262].

Pathophysiology

Migraine is a complex pathophysiological disease condition of the nervous system. There are several mechanisms that are emerging as the explanation of why seemingly unrelated symptoms and disorders appear in higher frequency in migraine patients. Several of these hypotheses have been mentioned in detail within the discussions of specific comorbidities, but this is a review of the broad categories of pathophysiologic phenomenon that potentially link migraine to its many comorbidities and auras.

Comorbidities occur alone and in many combinations, with and without headaches. Epidemiologic studies have pointed out frequent coexistence of multiple comorbidities in migraine sufferers. Examples of these clustered associations are (1) migraine, restless legs syndrome, and depression [96]; (2) allodynia, irritable bowel syndrome, chronic fatigue, fibromyalgia, and mood disorders [111]; (3) migraine, irritable bowel syndrome, fibromyalgia, sleep disorders, and syncope [253]; (4) vulvodynia, fibromyalgia, interstitial cystitis, temporomandibular pain, and irritable bowel syndrome [256–260]; (5) migraine, balance disorders and anxiety [263], migraine, childhood carsickness, allergies, and fatigue [37]; (6) interstitial cystitis, irritable bowel syndrome, dyspepsia, sleep disorders, fatigue, fibromyalgia, syncope, and migraine [253]; (7) migraine, phantosmia, and epileptic seizures [104]; (8) restless legs syndrome, photophobia, phonophobia, tinnitus, dizziness, neck pain, and temporomandibular pain [95]; and (9) migraine, temporomandibular pain, fibromyalgia, irritable bowel syndrome, interstitial cystitis, and restless legs syndrome [264]. It is the anatomically close relationship of the brainstem nuclei that is essential to the phenomenon of comorbid conditions.

Brainstem

While some of the overlap of different comorbidities occurs at the level of neurotransmitter dysfunctions in the periphery, the core of their pathophysiologic commonality appears to be seated in the brainstem. Within the subcortical nervous system, a number of complex interconnections appear to explain why people with migraine suffer from apparently unrelated other illnesses.

To illustrate the complex relationship of the brainstem nerve centers from the spinal tracts through the medulla, pons, and midbrain to the subcortical structures of the hypothalamus, thalamus, amygdala, and finally the cingulate nuclei and other cortical structures, let us follow some of the connections from the trigeminal nerve. Signals from the trigeminal ganglion enter at the level of the pons and activate the trigeminal nucleus. This collection of neural cell bodies is the long thin vertically oriented cranial nerve nucleus that spans the medulla, pons, and midbrain with axons projecting to adjacent periaqueductal gray, median raphe nucleus, vestibular nucleus, nucleus solitary, nucleus ambiguus, and superiorly to the locus coeruleus of the midbrain, superior salivatory nucleus, hypothalamus, and thalamus.

The locus coeruleus (LC) is the major noradrenergic nucleus of the brain and it is the hub of connections throughout the neuraxis using a variety of neurotransmitters. Its functions involve physiological responses (alertness) to stress and panic, as well as regulation of autonomic activity. The LC wakes up the brain through dense excitatory projections to the majority of the cerebral cortex, thalamus, serotoninergic dorsal raphe and cholinergic pedunculopontine, and laterodorsal tegmental nucleus. It has substantial inhibitory projections to sleep-promoting GABAergic neurons of the basal forebrain and ventrolateral preoptic area.

The importance of the LC in controlling autonomic function results from both direct projections to the spinal cord and projections to autonomic nuclei including the dorsal motor nucleus of the vagus, the nucleus ambiguus, the rostroventrolateral medulla, the Edinger–Westphal nucleus, the caudal raphe, the salivatory nuclei, the paraventricular nucleus, and the amygdala. LC activation produces an increase in sympathetic activity and a decrease in parasympathetic activity via these projections [265]. Hypersensitivity of this nucleus is also responsible for photophobia and phonophobia.

The trigeminal nerve has a direct connection to the superior salivatory nucleus. Its output travels along the greater petrosal (Vidian) nerve to synapse in the pterygopalatine ganglion where efferent nerves travel to the mucosal glands of the nose, palate, and pharynx. This explains the rhinorrhea associated with midfacial pressure and pain (trigeminal efferents).

The dorsal raphe nucleus (DRN) is a brainstem nucleus located in the midbrain and pons. For its widespread projections to many areas of the brain, its neurons utilize many transmitters (primarily serotonin) to control various physiological functions, including learning, memory, and affect [266]. Serotonin secreted from the dorsal raphe nuclei is implicated in both the control of sleep cycles and migraine (pain) pathogenesis [92]. The periaqueductal gray receives pain fibers from other sensory afferents and it is critical to pain modulation. Its neural fibers pass signals to the dorsal nucleus raphe where many autonomic activities are initiated. Together the locus coeruleus, dorsal raphe, and periaqueductal gray nuclei have the greatest influence over the perception of pain.

Adjacent to the trigeminal nucleus are the solitary tract nuclei that contain primarily motor efferent nerves but also second-order nerves join the postrema, a medullary structure that controls nausea and vomiting with other autonomic control centers. Neurons of the nucleus tractus solitarius (NTS) receive vagal sensory

information from cardiorespiratory and subdiaphragmatic organs of the gastrointestinal tract. There is input from the facial, glossopharyngeal and vagus nerves, and projections to the reticular formation, parasympathetic neurons, hypothalamus, and thalamus, forming circuits that contribute to autonomic regulation. NTS neurons comprise many intermixed cellular types scattered throughout the various NTS subnuclei with no apparent organization. This type of apparent dissociated organization makes it hard to identify with certainty the visceral inputs and function of specific neuronal populations.

Until recently the assumption was that the NTS comprised simple reflex pathways, such as regulating gastrointestinal motility and secretion. Evidence is now emerging that suggests that these pathways are contributing to the modulation of the neuronal systems of the hypothalamus and the enteric nervous system [267]. This neuronal network is integral in the nausea and vomiting that accompanies migraine attacks, but is also likely important in the genesis of colic, cyclical vomiting syndrome, abdominal migraines, and more. The NTS also handles information from the gustatory tracts and may be involved in burning mouth syndrome and dysgeusia. Electrophysiological studies reveal that the trigeminal nerve, which innervates sensation on the tongue, modulates the gustatory (taste) neurons arising from cranial nerve VII at the level of the solitary nucleus [268]. It has been observed that the areas responsible for urinary system and taste in the pons and cerebral cortex in the brain are close in proximity [269].

Ascending fibers via the spinothalamic tract activate the third-order trigeminovascular nociceptive neurons of the thalamus. The role of the thalamus in pain modulation, in conditions such as vulvodynia, is reinforced by the thalamic activity (and other brain areas) demonstrated during the premonitory phase [270] and headache phases [271] of migraine attacks.

Other neural connections to the hypothalamus, using serotonin as their neurotransmitter, play an important role in controlling sleep and pain. Moreover, the hypothalamus regulates the core temperature through links to the endocrine system [272].

The hypothalamic-pituitary-adrenal axis (HPA axis) is a complex set of direct influences and feedback interactions among three endocrine glands: the hypothalamus, the pituitary gland, and the adrenal glands. The interactions among these organs constitute the HPA axis, a major part of the neuroendocrine system that controls reactions to stress and regulates many body processes, including digestion, the immune system, mood and emotions, sexuality, and energy storage and expenditure. The HPA axis is implicated in the association of migraine with fatigue, fibromyalgia, irritable bowel syndrome, sleep disturbances, cognitive and memory impairment, dizziness, and ataxia.

The ascending connections reach to the cortex via input from the thalamus to the cingulate. The cingulate with its connections with the insula, amygdala, and orbitofrontal cortex forms the limbic system. The insula is associated with taste perception but it receives input from the entire body and is integral to emotional responses in general. The limbic system plays an important role in depression [273].

A preliminary study showed that painful trigeminal stimulation could induce an imbalance of the vestibular system in migraine patients and possibly explain their predisposition to vertigo [274].

The basal ganglia comprise multiple subcortical nuclei and integrate information from the cerebral cortex, thalamus, and brainstem, as well as several other brain areas. The basal ganglia affect pain processing may play a significant role in the pathophysiology of the episodic migraine.

Genetics

Inheritance of genetic material that affects the normal function of neuron transmission is one of the key factors that may link many of these comorbidities. Genome-wide association studies indicate that migraine susceptibility genes are involved in various pathways, including neurotransmission [275]. Specific genetic errors in ion-channel function and neurotransmitter production, sensitivity, and destruction have been identified. Although not all of the genetic errors responsible for migraine disease have been identified, the variety of known faulty alleles begins to explain the range and variability of migraine symptomatology.

Migraine genes are difficult to identify. Between 1996 and 2005, the first three genes in familial hemiplegic migraine were identified. They encode for three ion-channel transporters: a neuronal calcium channel (CACNA1A, FHM1), a glial sodium/potassium pump (ATP1A2, FHM2) and a neuronal sodium channel (SCN1A, FHM3). Mutations in CACNA1A and ATP1A2 facilitated the initiation of cortical spreading depression waves, the mechanism underlying the migraine aura, and most likely increased neuronal excitability with an excess of glutamatergic neurotransmission. In 2012, PRRT2 has been identified as the fourth FHM gene, and encodes an axonal protein associated to the exocytosis complex.

In the 1990s, family and twin studies showed that the more common varieties of migraine (migraine without aura and migraine with typical aura) were polygenic, with an overall heritability nearing 50%. These genetic factors interact with environmental factors. Since 2010, three large genome-wide association studies have identified six genetic variants associated with migraine. Each variant has only a modest contribution to the overall genetic risk of migraine, suggesting a marked genetic heterogeneity. Three of the migraine-associated variants affect genes involved in glutamate homeostasis. Another variant concerns a gene encoding a protein implicated in pain sensitivity. Three of the four polymorphisms (genetic variations) are associated both with migraine without aura and migraine with aura, supporting the existence of molecular mechanisms shared by all varieties of migraine. The vast majority of the migraine genes are still to be identified [276].

Overall, the genetic basis of migraine is still being worked out. Other studies have identified astrocyte- and oligodendrocyte-related genes that are involved in protein modification and signal transduction in migraineurs [275]. Other polymorphisms, involved in dopamine metabolism, are associated with hormonally

modulated migraine. Other neurotransmitters (serotonin, CGRP, noradrenalin, glutamate, GABA, substance P, nitric oxide, and melatonin) are also shared in the mechanism of migraine and other functions of the central nervous system.

And genetics have been linked to comorbid migraine conditions, including the familial vestibular disorders of motion intolerance and vestibular migraine (Frejo).

The full impact of genetic susceptibility on the development of migraine disease is not established with certainty.

Mitochondriopathy

Mitochondrial dysfunction leads to impaired oxygen metabolism [277] and migraineurs have been shown to have a reduction in mitochondrial phosphorylation potential in intervals between headaches [278]. It has been speculated that mitochondriopathy is the common etiology of migraine and cyclic vomiting syndrome. This theory is the basis for the use of supplements that enhance mitochondrial function in the treatment of migraine, such as riboflavin, coenzyme Q10 (CoQ10), and alpha lipoic acid.

Response to Migraine Medication

Another argument that a common pathophysiology underlies the association of migraine with its comorbidities is the effectiveness of migraine medicines for both conditions. Topiramate, one of the most effective medications in the control of migraine, is an anti-epileptic drug [163]. Tricyclic antidepressants, another mainstay of migraine and depression prevention, are effective for irritable bowel syndrome and functional dyspepsia [227]. Cyclic vomiting syndrome responds positively to triptans [232]. Tricyclic antidepressants, tramadol, gabapentin, and duloxetine are effective with both migraine and gastroparesis [235]. Migraine and fibromyalgia share dramatic defects in the serotonergic and adrenergic transmission systems. Both conditions improve with the combination of monoamine-oxidase inhibitors with 5-HTP [191].

Cortical Spreading Depression

A common feature of migraine and its comorbities is their chronic nature, but then interspersed with acute symptoms. For acute migraines, the mechanism is often explained by the phenomenon of a cortical spreading depression. The genetically predisposed central nervous system is overly reactive but it does often require a trigger. This can be external stimulus, such as a bright light or a certain dietary

component, or an internal disturbance, such as a barometric change, sleep disturbance, or stress. Once the trigeminal nucleus has been activated, signals are sent throughout the brainstem and trigger prodrome, followed by the cortical spreading depression across the cortex. This electrical wave sets off the release of many vasoactive and inflammatory agents (cytokines, such as interleukins, tumor-necrosis factors, matrix-metalloproteinase, C-reactive proteins and alpha-interferon produced by macrophages, mast cells, endothelial cells, and more) and, once the painful headache dissipates, the inflamed and activated central nervous system passes through the postdromal recovery period where the injured brain must slowly recover over the next day or two. The repeated acute events of cortical spreading depression followed by neuroinflammation are implicated in the development of central sensitization and chronic forms of migraine, including insulin resistance, obesity, arteriosclerosis, stroke, and brain white matter lesions [279–281]. This neuroinflammatory process has a systemic effect on the vascular endothelial function that explains the higher risks for impaired vascular function [282] and other comorbid conditions within and beyond the central nervous system.

White Matter Signal Abnormalities

MRI scans of migraine patients reveal a higher incidence of white matter signal abnormalities [283]. The hyperintensities appeared most frequently in the deep white matter of the frontal lobe with a similar average hyperintensity size in all hemispheric lobes. Any history of severe headache can be associated with an increased volume of white matter hyperintensities.

Several mechanisms of acute repeated migraine have been proposed in the lesion development, but the predominant theory is repeated migraine attacks with its neuroinflammatory response leads intracerebral hemodynamic changes. MRI studies have suggested that within the white matter hyperintensity lesion are tissue damage with axonal loss, low glial cell density, and an enlarged extracellular space with an increased extracellular water fraction. These features might be the consequences of microvascular ischemic changes during repeated migraine attacks [284].

But these vascular changes in the cortex should be distinguished from brain infarcts. Migraine with aura has been the only headache type associated with brain infarcts. And there has been no evidence that headache of any type by itself or in combination with white matter hyperintensities was associated with cognitive impairment [285].

This longitudinal MRI study found clinically silent brain white matter hyperintensities to be predominantly progressive in nature. (Erdelyi-Botor) In a study over a 9-year period, women with migraine had a higher incidence of deep white matter hyperintensities but did not have significantly higher progression of other MRI-measured brain changes. There was no association of migraine with progression of any MRI-measured brain lesions in men [286, 287]. Small white matter hyperintensities in patients with a low migraine attack frequency had a higher

chance to disappear than large white matter hyperintensities or white matter hyperintensities in patients with a high attack frequency [288].

Hormonal Influence

Rises and falls in levels of sex hormones appear to potentiate the vulnerable neural circuitry of a migraineur. Estrogen and progesterone receptors are found throughout cortical and subcortical structures in the brain. Estrogen can bind to nuclear estrogen receptors to alter gene transcription through genomic effects or can bind to cell membrane receptors to exert other cellular effects [289].

The important relationship of female sex hormones in migraine has been recognized in its effect on the tripling of migraine prevalence among women during puberty, the affect of menstruation on a subset of migraineurs, the variable symptomatology experienced by many women during pregnancy and finally the reduction in migraine headaches after menopause. But many questions about how fluctuations in sex hormones during menopause may shift the symptomatology of migraine from predominantly a headache disorder to a range of migraine comorbid symptoms, including balance difficulties, midfacial pressure and autonomic symptomatology, cognitive deficiencies, sleep disturbances, thermoregulation, and burning mouth syndrome, are only currently being raised.

While the full role of female sex hormones in migraine is not established, the mechanisms underlying these relationships are even more poorly understood. Beyond the universal effects of sex hormone fluctuations on women, sex hormones may modulate expression of nociceptive mediators, such calcitonin gene-related peptide (CGRP), and thereby may regulate trigeminal nerve sensitization [290]. Estradiol also increases neuronal sensitivity by augmenting N-methyl-D-aspartate-mediated glutamate receptor activity [291]. Sex hormones may further modulate genetically sensitive neurotransmitters [292]. The identification of several genetic polymorphisms (meaning more than one allele—one of two or more alternative forms of a gene—for a specific trait that is common enough that it cannot be explained by merely an occasional independent mutation) adds to the evidence that there is a distinct phenotype of hormonally modulated migraine [293]. It has been speculated that the combination of sex hormones and genetic susceptibility are critical factors in 34–57% of migraineurs [294]. But the lack of female animal studies has limited our current understanding of sex hormonal effects [295, 296].

Conclusion

There does not appear to be a single simple explanation for the occurrence of migraine comorbidities. Some of these migraine-related symptoms, such as vestibular migraine, phantosmia, and burning mouth syndrome are described as

migraine “auras”, but they present predominantly independent of a headache, last for long periods of time and often occur later in the lives of women. A better pathophysiological model is that of allodynia, where the neuroinflammation associated with early attacks of migraine evolves in the more chronic and constant form of central sensitization. Clearly the diversity and variability of symptoms belies a complex neurobiology involving genetics, multiple neurotransmitters, vasoactive, and neuroinflammatory processes at multiple neuroanatomical sites [297].

While the details about the commonalities between migraine comorbidities are far from being understood, the similarities between these medical conditions do provide a shadowy outline of a neurological condition that extends broadly across the nervous system.

A familiarity with migraine comorbidities can open one’s mind to the broad effects of migraine on the central nervous system. Rather than the narrow association of migraine disease with headaches, one can appreciate it as a complex, evolving hypersensitivity disease of the nociceptive (pain) and other pathways of the subcortical brain.

Moreover, an appreciation of migraine comorbidities raises innumerable questions that are waiting to be answered. The complexity of migraine pathophysiology makes one appreciate that to understand this common disease is a foundation to understanding a large portion of brain function. And the search for answers to other neurological diseases, such as chronic traumatic encephalopathy, will help to find the mechanisms underlying migraine. These challenges should fire the imagination of another generation of researchers and inspire clinicians to continue to look for new explanations for age-old symptoms.

And, on a more practical level, an appreciation of comorbid migraine disorders can immediately impact most clinician’s patient care.

(1) Ask about migraine-related disorders in your history-taking or patient intake form or symptom questionnaire. Carsickness, family history of migraine, anxiety, and depression are all red-flags for migraine
(2) Look for comorbidities in migraineurs. Use knowledge about comorbidities to screen for migraine disease and influence the choice of medications. For example, the use of amitriptyline as a migraine preventive medication also may address a patient’s insomnia.
(3) Comorbidities may influence the clinical course and prognosis. For example, migraineurs with depression and anxiety have worse prognosis for their quality of life and response to treatment. The larger the number of comorbidities correlates with the intensity and pain duration of temporomandibular pain [265]. More comorbid migraine symptoms lead to a worse quality of life [95].
(4) Some comorbidities are valuable in understanding how malfunctioning sensory neurons can explain less intuitive symptoms, such as ear pressure, foreign body sensation in the ear, and unresponsive conditions such as sinusitis, benign positional vertigo, and Meniere’s disease.

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Chapter 10
Surgery for Migraine: An Evidence-Based Review

Ibrahim Khansa and Jeffrey E. Janis

Introduction

Migraine headaches are believed to result from irritation of the trigeminal nerve, leading to dural inflammation [1]. This is mediated by factors such as calcitonin gene-related peptide, substance P, and neurokinin A [1–3]. According to the peripheral theory of migraine headaches, peripheral noxious stimuli irritate branches of the trigeminal nerve, or cervical nerves and trigger the central events [4]. Patients suffering from migraine headaches often have point tenderness precisely overlying a trigger point at which a sensory nerve is compressed by muscle, fascia, artery, or bone [5].

The peripheral theory of migraine headaches is validated by the efficacy of both botulinum toxin (which temporarily weakens muscles that compress sensory nerves involved in migraine pathogenesis), and surgical trigger point decompression. The latter has been proven to be efficacious by numerous studies [6–12], including a prospective randomized trial using sham surgery as a placebo control [10].

In this chapter, the diagnostic methods commonly used in the localization of the trigger site or sites responsible for the migraine headaches are delineated. The anatomy of the compression points of the frontal, temporal, occipital, nasal and atypical trigger sites are then described. This is followed by a description of the different procedures to decompress those trigger points, and a summary of the published clinical outcomes of surgical decompression.

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Trigger Site Localization

The surgical treatment of migraine headaches is indicated for patients with chronic migraines diagnosed by a neurologist, refractory to medical treatment. Once chronic migraine headaches are diagnosed, the accurate identification of the peripheral trigger site(s) involved is essential to obtaining successful outcomes with surgical decompression.

The first step in trigger site localization is a detailed history. This helps with migraine localization in two ways. First, most patients will, when asked, be able to pinpoint with one finger the location where their migraine headaches begin [13]. Second, an accurate history of the nature and timing of the headaches, as well as their exacerbating, ameliorating, and associated factors, may elucidate a pattern that fits known constellations of symptoms. For example, patients with headaches originating from a nasal trigger site often have headaches that originate behind the eyes, typically in the morning, exacerbated by menstrual periods and alleviated by nasal decongestants [14].

The second step is physical examination. Digital pressure over a suspected trigger site may reveal tenderness. An intranasal examination may reveal mucosal contact points leading to migraine headaches. Finally, handheld Doppler examination over a suspected auriculotemporal, lesser occipital or atypical trigger site may reveal an arterial signal, indicating arterial compression of a sensory nerve branch as a likely source of migraines, or even potential arteritis.

Patients who present with an active migraine headache offer an opportunity for the use of diagnostic nerve blocks: a small amount of local anesthetic is injected precisely into the suspected trigger site. Resolution of the migraine headache is diagnostic of the trigger site. However, an ineffective nerve block does not always rule out a peripheral trigger site as the trigeminal tree may already be inflamed from a long-standing headache by the time the block is performed.

Patients who present without an active headache, and with suspected muscular compression of a nerve, are good candidates for diagnostic botulinum toxin A injection. The toxin is injected into the corrugator supercilii muscle (in the case of a suspected frontal trigger site), the temporalis muscle (in the case of a suspected zygomaticotemporal trigger site), or the semispinalis capitis muscle (in the case of a suspected central occipital trigger site). Improvement in migraine headache intensity, frequency, and duration over the following weeks to months helps identify the injected trigger site as contributory to the headaches.

Finally, in patients with a suspected rhinogenic trigger site, computed tomography imaging may reveal mucosal contact points, septal deviation/spurs, turbinate hypertrophy, and/or concha bullosa.

Frontal Trigger Site

The frontal migraine trigger site includes the supraorbital (SON) and supratrochlear (STN) nerves.

Compression Points

The first potential compression point of the SON is the foramen or notch through which it exits the orbit. A notch is present 83% of the time, and located 25 mm lateral to the midline [15]. A foramen is present 27% of the time, and located 31 mm lateral to the midline [16–18]. In 10% of patients, both a foramen and a notch are present [19].

The SON then divides into a superficial and deep branch. In 78% of individuals, one or both of these branches travel through the corrugator supercilii muscle (CSM) [20, 21], which extends from 3 mm lateral to the midline to 85% of the distance to the lateral orbital rim, with its apex 33 mm above the nasion at the level of the lateral limbus [20]. In 40% of individuals, the branches off the deep branch of the SON alone travels through the CSM. In 34% of individuals, branches off both the superficial and deep branches of the SON travel through the muscle. In 4% of individuals, only branches off the superficial branch travel through the muscle, and in 22% of individuals, no branches of the SON travel through the muscle [21]. The SON fibers may then be compressed more superiorly by the interdigitations of the horizontal CSM fibers with vertical frontalis muscle fibers [21].

The first potential compression point of the STN is the supratrochlear notch (present in 72% of individuals) or foramen (28% of individuals) [22]. This compression point is located 16 to 23 mm lateral to the midline [6]. When a foramen is present, it is located 4 mm cranial to the superior orbital rim [22]. The STN then divides into two branches after exiting the orbit. In 84% of individuals, both branches travel through the CSM (18.8 to 19.6 mm lateral to the midline), exiting it 15 mm cranial to the superior orbital rim [22]. In 4% of individuals, only one branch of the STN travels through the CSM. In 12% of individuals, no branches of the STN travel through the CSM.

As the STN travels further superiorly, it may also be compressed by the interdigitations between the horizontal CSM fibers and the vertical frontalis muscle fibers [21].

Surgical Decompression

There are three described approaches to decompress the frontal trigger site. For symmetry purposes, these procedures are usually performed bilaterally.

In a transpalpebral approach, a standard upper blepharoplasty incision is used. Dissection is continued through the orbicularis oculi muscle, to reach the plane just superficial to the orbital septum. Dissection is then carried superiorly in this plane until the superior orbital rim is reached. The SON and STN are identified as they exit the orbit through notches or foramina. Osteotomies can be performed to turn any foramina into wide-mouthed notches. The supraorbital and supratrochlear arteries and veins may need ablation if they abut or compress the nerves. Limited intraconal dissection of both nerves should also be performed in order to make sure that no bony compression remains [23]. The corrugator supercilii and depressor supercilii and procerus muscles are then excised using bipolar electrocautery. A fat graft is usually used to replace the volume of those excised muscles.

In an endoscopic approach, the brow is accessed through four to six endoscopic ports, which are sagitally oriented and located behind the hairline. One incision is marked centrally, two paramedian incisions are marked approximately 7 cm lateral to the midline on each side (medial to the temporal crest), and two temporal incisions are marked approximately 10 cm lateral to the midline on each side (lateral to the temporal crest, approximately 3 cm lateral to the paramedian incisions). The central and paramedian incisions are carried to the subperiosteal plane, and the temporal incisions are carried to the deep temporal fascia. A periosteal elevator is then inserted into each temporal incision to release the temporal fusion line. Subperiosteal dissection is performed from cranial to caudal toward the superior orbital rims bilaterally. About 1 cm above the rim, the periosteum is incised, revealing the corrugator muscle. The supraorbital and supratrochlear artery and vein are ablated. The SON and STN are carefully dissected, and the CSM is excised completely in piecemeal fashion with an endoscopic grasper (Fig. 10.1). If a foramen is present, it may be addressed through a separate upper eyelid stab incision with a 2 mm osteotome, with direct endoscopic visualization.

In the direct brow approach, an incision is made along the medial two-thirds of the upper border of the brow. Dissection is carried through the orbicularis oculi muscle, then cranially in the plane deep to the orbicularis oculi muscle and superficial to the orbital septum. The remainder of this procedure is similar to the transpalpebral approach described above.

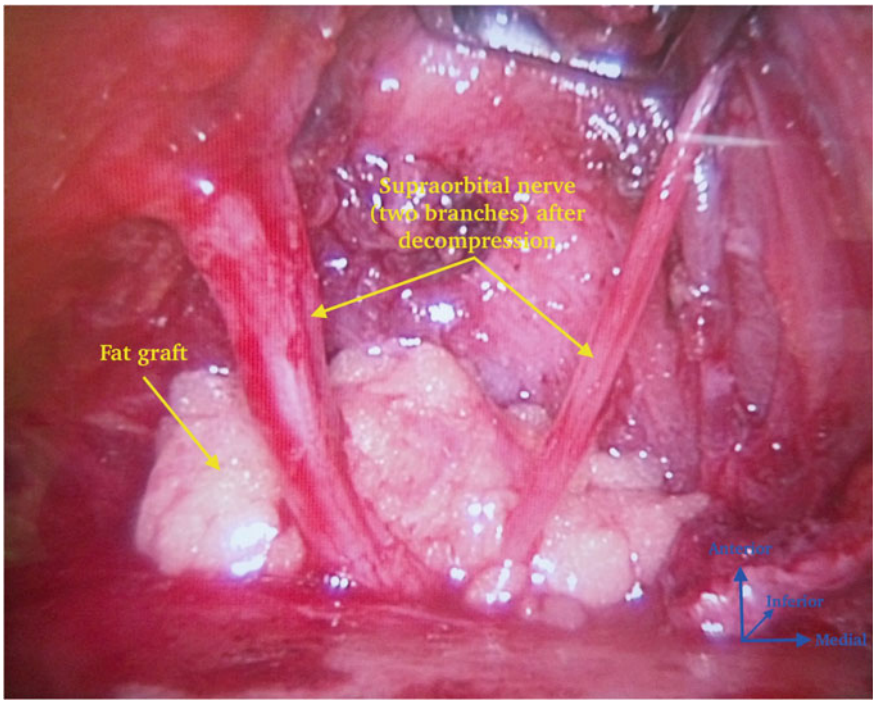

Fig. 10.1 Endoscopic visualization of the supraorbital nerve (two branches) after decompression. A fat graft is used to buttress the nerve branches and to replace the volume of the excised corrugator, procerus and depressor supercilii muscles

Outcomes of Decompression

Multiple studies have examined the clinical outcomes of surgical decompression of the frontal trigger site [7–12]. Complete migraine elimination has been reported in 35% [12] to 64% [9], and elimination or significant improvement in 79.5% [8] to 99% [9].

Temporal Trigger Site

The temporal compression point includes the zygomaticotempotal (ZTN) and auriculotemporal (AT) nerves. In 13–40% of individuals, the ZTN and AT have interconnecting branches [24, 25].

Compression Points

The first potential compression point of the ZTN is the foramen through which it exits the orbit and enters the temporal fossa [26], located 6.7 mm lateral to the lateral orbital rim, and 7.9 mm cranial to the nasion.

The second potential compression point of the ZTN occurs as it travels through the temporalis muscle. This occurs in 50% of individuals [24]. In the remaining 50%, the ZTN courses between the temporal periosteum and the temporalis muscle before piercing the deep temporal fascia 16.9 mm lateral and 6.5 mm cranial to the lateral palpebral commissure [25]. The sentinel vein is a reliable landmark for locating the ZTN: The ZTN is usually found approximately 1 cm lateral and 0.5 mm caudal to the sentinel vein [27].

The first two compression points of the AT are both fascial bands, which occur 13.1 mm anterior and 5 mm cranial to the anterosuperior external auditory meatus [28] (present in 100%), and 11.9 mm anterior and 17.2 mm cranial to the anterosuperior external auditory meatus (present in 85%).

In 80% of individuals, the AT intersects with the superficial temporal artery [29]. which constitutes the third potential compression point. The intersection is simple in 81.2% of cases (19.2 mm anterior and 39.5 mm superior to the anterosuperior external auditory meatus) and helical in 18.8% (between 20.0 mm and 24.7 mm anterior, and 53.7 mm and 62.7 mm cranial to the anterosuperior external auditory meatus) [27, 30].

Surgical Decompression

There are three described approaches to the decompression of the ZTN.

In an endoscopic approach, when combined with the SON and STN decompressions previously described, the same four to six sagittally oriented incisions are marked behind the hairline. The ZTN can be accessed without additional incisions in this fashion. If addressed in isolation, however, the central incision(s) are not created. Instead the paramedian and temporal incisions will suffice. The temporal access incision is used to dissect along the superficial surface of the deep temporal fascia, from cranial to caudal, until the superficial temporal fat pad is visualized about 2 cm cranial to the zygomatic arch. The superficial layer of the deep temporal fascia is incised, and that layer and the underlying superficial temporal fat pad are elevated, continuing caudal dissection along the deep layer of the deep temporal fascia, to the lateral orbital rim. The sentinel vein is identified and controlled (if necessary). The ZTN can be identified about 1 cm lateral and 0.5 mm caudal to the sentinel vein [26]. The ZTN is separated from its associated artery in order to control them individually. The zygomaticotemporal artery is ablated with cautery. The nerve can either be decompressed (by widening its entry and exit point into the deep temporal fascia/temporalis muscle) [31], or avulsed by applying traction to it, allowing its proximal end to retract into the temporalis muscle.

In a transpalpebral approach, described by Austen and Gfrerer [32], a standard upper blepharoplasty incision is made, and dissection is performed in a preseptal plane to the lateral orbital rim. The plane just superficial to the deep temporal fascia is dissected. This allows identification of the sentinel vein and ZTN just lateral to the lateral orbital rim. The nerve is then decompressed or avulsed, as described above.

In a modified Gillies approach, described by Peled [33], a single, larger 3.5 cm incision is made 5–7 mm posterior to the temporal hairline, and taken to the deep temporal fascia. The plane just superficial to the deep temporal fascia is dissected under direct visualization toward the lateral canthus, until both the sentinel vein, and the ZTN and its associated artery are visualized. The nerve is then decompressed or avulsed, as described above.

Decompression of the AT is usually performed via a direct approach. The patient is asked to use an indelible marker to place a mark over the point of maximal tenderness during a migraine attack. A handheld Doppler is used to confirm the presence of an arterial signal at that point [34], indicating an anterior branch of the superficial temporal artery. A small incision is made directly over the mark. This will allow identification of the main trunk or a branch of the AT. Its relationship to the superficial temporal artery and vein is assessed, and the nerve is decompressed by ablating any neighboring or crossing branches of the artery and vein (Fig. 10.2).

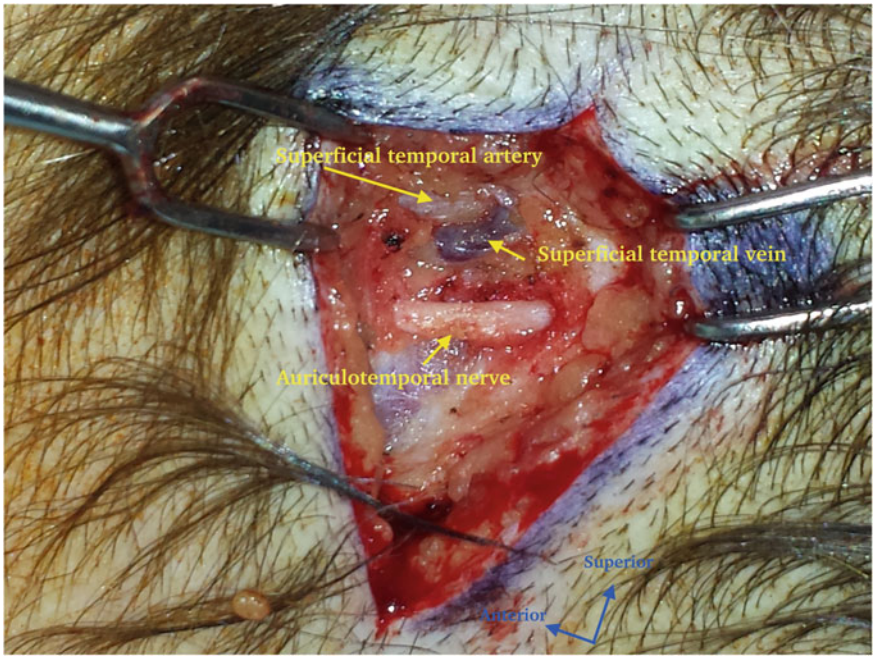

Fig. 10.2 Visualization of the auriculotemporal nerve, in close proximity to branches of the superficial temporal artery and vein

Outcomes of Decompression

Multiple studies have examined the clinical outcomes of the decompression of the ZTN [9, 10, 12, 30, 35]. Complete migraine elimination has been reported in 52.6% [12] to 63% [9] of patients, and significant improvement or elimination has been reported in 85% [34] to 100% [10].

Occipital Trigger Site

The central occipital trigger site includes the greater occipital (GON) and third occipital (TON) nerves, and the lateral occipital trigger site consists of the lesser occipital nerve (LON).

Compression Points

The first compression point of the GON occurs as it interacts with fascial bands between the obliquus capitis muscle and the semispinalis capitis muscle. This is located 77.4 mm caudal and 20.1 mm lateral to the external occipital protuberance (EOP) [36]. The second compression point, present in 90% of individuals [37], occurs when the GON enters the deep surface of the semispinalis capitis muscle. This occurs 59.7 mm caudal and 17.5 mm lateral to the EOP [35]. The third compression point occurs as the GON exits the superficial surface of the semispinalis muscle, 34.5 mm caudal and 15.5 mm lateral to the EOP [35, 38, 39]. The fourth compression point occurs as the GON enters the trapezius tunnel 21 mm caudal and 24 mm lateral to the EOP [35]. The fifth compression point occurs as the GON pierces the trapezius tendon 4.4 mm caudal and 37.1 mm lateral to the EOP [35]. The sixth potential compression point of the GON, present in 54% of individuals, is the occipital artery. When this is a simple intersection, it is 10.7 mm caudal and 30.3 mm lateral to the EOP. When it is a helical intertwining, it is 24.9 to 1 mm caudal, and 25.3 to 42.1 mm lateral to the EOP [35].

The potential compression point of the TON occurs as it emerges from the superficial aspect of the semispinalis capitis muscle. This is located 61 mm caudal to the inferior external auditory canal, and 13 mm lateral to the posterior midline [40].

The first potential compression point of the LON occurs as it emerges from the sternocleidomastoid (SCM). This is located along the posterior border of the SCM in 86.7%, and through the SCM in 13.3% [39]. This compression point is located 53.2 mm caudal to the inferior external auditory canals, and 61–69 mm lateral to the posterior midline [39, 41]. The second compression point of the LON is its intersection with the occipital artery, present in 55% of individuals 20 mm caudal to

the anterosuperior external auditory canals, and 51 mm lateral to the posterior midline [40]. This is a simple crossing in 82% of cases, and a helical intertwining in 18%. The third compression point of the LON is a fascial band, present in 20% of individuals, located 13.1 mm inferior to the anterosuperior external auditory canals, and 47 mm lateral to the posterior midline [40].

Surgical Decompression of the Central Occipital Site (GON and TON)

A 4 cm vertical incision is made in the posterior midline, within the hairline. Dissection is made directly to the median raphe of the trapezius muscle. The skin and subcutaneous tissue are then elevated off the trapezius muscle bilaterally for 1 cm. The trapezius fascia and trapezius muscle are then incised 1 cm lateral to the midline, revealing the underlying vertically oriented fibers of the semispinalis muscle. The TON and GON are then both identified in the plane between the semispinalis capitis and trapezius muscles (Fig. 10.3). The TON is usually avulsed, allowing its proximal end to retract into muscle. The GON is decompressed from inferior to superior, starting with the release of the obliquus capitis muscle and its associated fascial bands. Subsequently, a rectangular portion of the semispinalis capitis muscle medial to the GON, and a triangular portion lateral to the GON, are

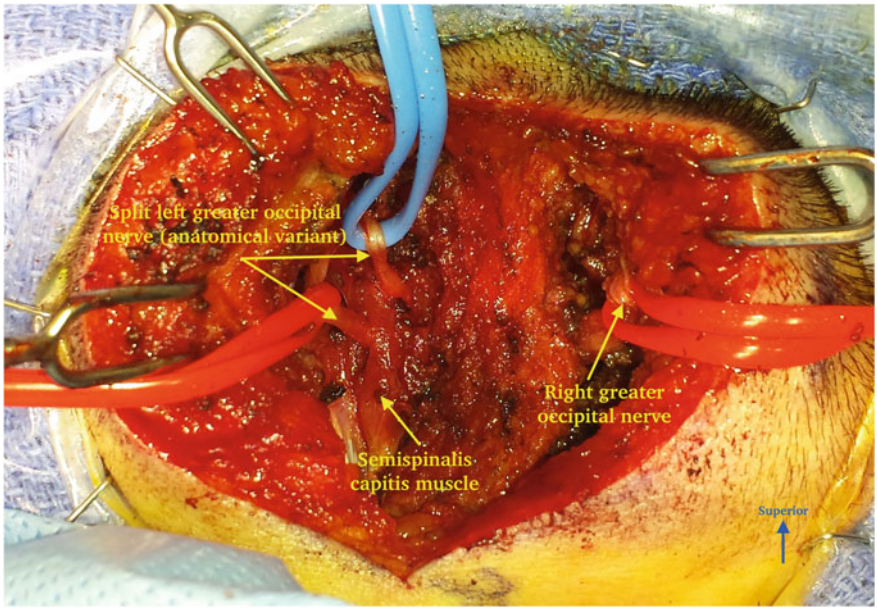

Fig. 10.3 Bilateral greater occipital nerves, with an anatomical variant split nerve on the left

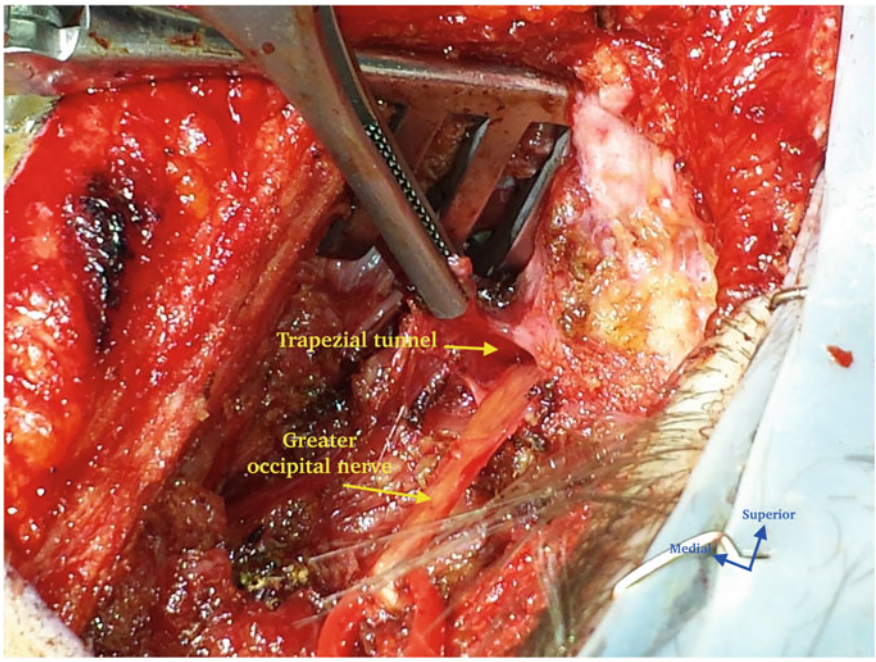

Fig. 10.4 The greater occipital nerve as it enters the trapezial tunnel

resected in order to relieve compression of the GON by this muscle. The trapezial tunnel and the nuchal fascia surrounding the GON are then lysed (Fig. 10.4), and if an intersection between the nerve and the occipital artery is present, the artery is ablated using cautery. A three-sided flap of fat is then developed and transposed under the nerve to the median raphe.

Surgical Decompression of the Lesser Occipital Site (LON)

The patient is asked to use an indelible marker during a migraine attack to indicate the site of maximal tenderness in the posterior lateral neck region. A handheld Doppler is used to verify the presence of an arterial signal at that site.

There are two potential approaches to the LON. If the GON and/or TON are being decompressed concurrently, the LON can be accessed through the midline incision, although this can be more difficult. Dissection is performed in a lateral direction to the point previously marked by the patient. The LON can usually be identified in the subcutaneous tissue. The nerve is traced proximally and distally. Proximally, if it pierces the sternocleidomastoid (SCM), a segment of surrounding SCM may be resected. Distally, if it intersects with a branch of the occipital artery, that branch is dissected free from the LON and ligated using bipolar electrocautery.

If the LON is being decompressed in isolation (the senior author's preferred approach), or if the trigger site is too lateral to be accessed through the midline incision, a small incision is made directly over the mark indicated by the patient, and the nerve is decompressed as described above.

Outcomes of Decompression

Multiple studies have examined the clinical outcomes of GON decompression [9, 10, 12, 41]. Complete migraine elimination has been reported in 43.4% [42] to 62% [9] of patients. Significant improvement or complete elimination has been reported in 80.5% [41] to 100% [9].

There are few clinical studies reporting outcomes of LON and TON release, and most patients in those studies underwent concomitant greater occipital nerve release [43].

Nasal Trigger Site

Compression Points

The nasal trigger site is due to intranasal mucosal contact points, which cause irritation of branches of the trigeminal nerve [44]. These are usually between the septum and the superior or middle turbinate [45]. A pneumatized turbinate (concha bullosa) may also lead to a contact point with the septum (Fig. 10.5) [46].

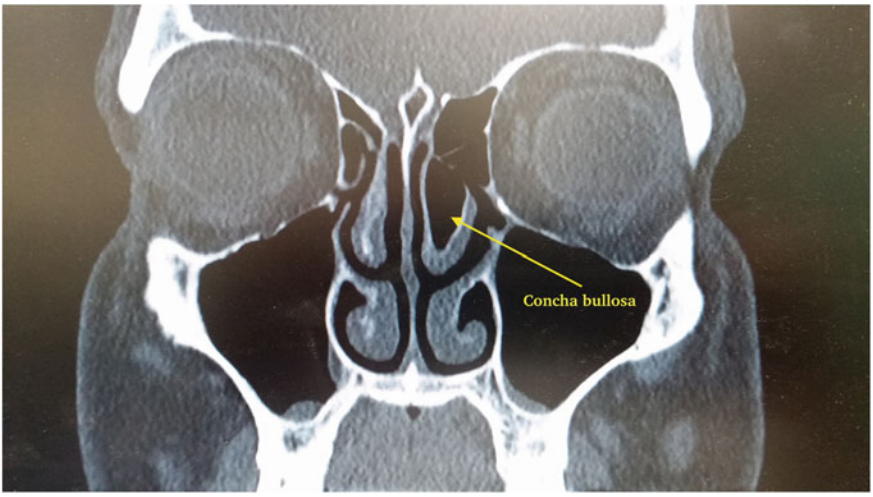

Fig. 10.5 Pneumatized left middle turbinate (concha bullosa)

Surgical Decompression

Depending on the specific inciting contact point, decompression of the nasal trigger site may consist of septoplasty, turbinate reduction, or both.

The septum is accessed through a modified Killian incision 1 cm posterior to the caudal border of the septum, followed by subperichondrial dissection of the quadrangular cartilage to the perpendicular plate of the ethmoid. A cartilaginous L-strut with 10 mm caudal and anterior limbs is preserved, and the remaining cartilage is resected. Remnants of the perpendicular plate are then removed.

The turbinate is accessed through a small mucosal incision, through which submucosal dissection is performed. A microdebrider is used to reduce the size of the turbinate head, and outfracture of the turbinate is performed with a Vienna speculum. A similar approach is used for the treatment of concha bullosa, medializing the middle turbinate after decompression.

Outcomes of Decompression

Multiple studies have examined the clinical outcomes of nasal trigger site decompression [9, 10, 12, 43, 47]. Complete migraine elimination has been reported in 34% [9] to 62.5% [12] of patients. Significant improvement or elimination has been reported in 65% [48] to 100% [12] of patients.

Atypical Trigger Sites

Compression Points

Other trigger sites may be present, but are quite variable between individuals and have not been fully studies with cadaver dissections. These trigger sites often consist of a small nerve branch compressed by a blood vessel. They are best identified by asking the patient to point with one fingertip at the site of maximal tenderness, where the headache begins. They can be confirmed with an arterial Doppler signal over the point indicated by the patient.

Surgical Decompression

Surgical decompression of an atypical trigger site is similar to that described for the auriculotemporal nerve. A small incision is made over the point indicated by the patient and the Doppler signal, and the compressed nerve is identified. Vascular

structures neighboring or crossing the nerve are then ablated with cautery, and any fascial bands are released.

Summary

Numerous cadaver and clinical studies have delineated the precise location of the compression points involved in the pathogenesis of migraine headaches. Accurate diagnosis of the trigger site or sites responsible for the migraine headache, coupled with complete surgical decompression of those sites, can achieve migraine headache resolution or significant improvement in the vast majority of patients with refractory, chronic migraine headaches.

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Chapter 11
Adjunctive and Integrative Therapy in Migraine Management

Jiahui Lin and Sezelle Gereau Haddon

Introduction

According to the 2012 National Health Interview Survey (NHIS), 33.9% of adults and 12% of children have used approaches to medical care that are considered outside of those typically practiced in standard Western medicine [1]. These approaches are often interchangeably referred to as complementary or alternative medicine (CAM). More precisely defined, complementary medicine refers to a therapy used *in addition to* standard Western medicine, while alternative medicine refers to a practice used *instead of* traditional Western medical care [2]. In December of 2014, The National Center for Complementary and Alternative Medicine (NCCAM) suggested the term "integrative health" be used instead of "alternative medicine", changing its own name to the National Center for Complementary and Integrative Health (NCCIH). NCCIH noted that large population based studies had demonstrated that the sole use of practices that have no scientific proof is actually rare. More commonly, patients combine complementary approaches with conventional treatment [3]. The American Board of Integrative Medicine has offered sub-specialty certification for fellows since 2014 [4].

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Of the patients included in the 2009 NHIS, 27.4 million US adults reported suffering from migraine or severe headache within 3 months of the survey date. Approximately one half of these (49.5%) used at least one CAM therapy in the year prior. Overall, it is believed that up to 82% of patients with headaches use integrative therapies, sometimes at the recommendation of allopathic practitioners. Only one half of these patients disclosed this use to their medical providers. Mind/body therapies were the most frequently used, followed by biologically based therapies, including herbs and supplements. Combining herbs, vitamins, and supplements (nutraceuticals) with conventional medications leads to more success than using nutraceuticals alone [5, 6].

The American Academy of Neurology (AAN) and the American Headache Society (AHS) published guidelines for various aspects of migraine prevention using a defined classification scheme for therapeutic questions [7]. Complementary therapies were initially reviewed in 2000 and updated in 2012 [8, 9]. Behavioral and physical treatments were last reviewed in 1998 [10]. Levels of evidence of the therapies from these guidelines are summarized below. The authors have updated it for this chapter to include all therapies discussed herein. Therapies included in the Holland et al. review [9] are in bold.

AAN evidence level A: established as effective, with at least 2 Class I studies:

Petasites
Acupuncture
Relaxation Training
Biofeedback
Cognitive Behavior Therapy

AAN evidence level B: established as probably effective with at least 1 Class I or 2 Class II studies:

Magnesium
MIG-99 (feverfew)
Riboflavin
Exercise

AAN evidence level C: established as possibly effective with at least 1 Class II or 2 Class III studies:

Co-Q10
Phytoestrogens
Chiropractic Therapies
Massage
Hyperbaric Oxygen Therapy
Hypnotherapy

AAN evidence level U: Inadequate or conflicting data:

Melatonin
MVI B6, 9, 12

Omega-3 Fatty Acids
Cannabinoids
Diet
Class I studies: Randomized, controlled trials in representative populations.
Class II studies: Randomized, controlled trials with incomplete data or inadequate controls; or prospective cohort studies.
Class III studies: All other controlled trials, including those in which patients serve as their own controls.

Nutraceuticals

A list of nutraceuticals discussed in this chapter, including dosages, specific brands, and side effects is summarized in Table 11.1.

Petasites *(Butterbur)—Level A Evidence*

Certain plants of the *Petasites* genus have properties that would make them appropriate for management of migraine. There are proven antihistamine, antileukotriene, and calcium channel blocking effects in various *Petasites* species. The sesquiterpenes petasin and isopetasin are thought to be the active ingredients. Because of these properties, *Petasites* would appear to be an ideal product for use in patients with allergy and migraine, or the classic "sinus headache" [11, 12].

A number of clinical trials suggest that the use of 150 mg of *Petasites* for a minimum of 3 months is useful in the prevention of migraine headaches [11, 13, 14, 15]. One small pediatric randomized control trial (RCT) showed efficacy in 19 patients (50–100 mg) only in weeks 40–48 [16]. The AAN and AHS have graded this product as level A evidence, though the German, Austrian, and Swiss headache societies and the German Society of Neurology have reviewed it less favorably. A 2004 review published in Otolaryngology Head and Neck Surgery gives it a moderate rating and suggests that more research is appropriate [17].

While *Petasites* appears to be effective in prevention of migraines, there are safety concerns, specifically regarding hepatotoxicity and carcinogenicity [18]. Many of the RCTs have used the brand Petadolex, produced by a German company. The product is produced utilizing a patented technique to remove toxic pyrrolizidine alkaloids (PA) from the rhizome of the plant. This extraction process utilized a methylene chloride solvent that was subsequently changed to a supercritical carbon dioxide (CO_2) process thought to be superior. Approval for Petadolex was initially granted by the German Health Regulatory Authority with the first solvent and withdrawn when the new extraction process was resubmitted for registration, as it was considered different than the original. In 2012, the

Table 11.1 Nutraceutical dosing information

Nutraceutical	Preferred formulation	Dose/time	Side effects	Precautions, interactions, contraindications
ALA		300–600 mg/d/3 mo	Rare, case reports	Possible hypoglycemia. May interact with antidiabetes, thyroid drugs or chemotherapeutic agents.
B2 Riboflavin		200–400 mg/d	Polyuria, diarrhea	
B3 Niacin	Oral, Sustained release (SR), IV	300–500 mg oral/d SR- 750 mg oral/d IV- 100–300 mg until flushing for 15 min	IV-abdominal cramping, vomiting, skin burning. Oral-flushing, pruritis, nausea, and vomiting.	Hepatotoxicity with sustained release formulations.
B6 Pyridoxine		25 mg/d	Rare—photosensitivity, nausea, asthma exacerbation	Doses over 200 mg have produced reversible neuropathy.
B9 Folic Acid		2 mg/d	Rare—nausea, bloating, depression	Possible interaction with Primidone, Pyrimethamine, Mysoline, Daraprim.
B12 Cobalamin		400 mcg/d	Rare—rash, acne, nausea, dysphagia	
Cannabis	Unclear—vaporized, edible, topical and smoked	≥once daily	Drowsiness	
CoQ10		1–3 mg/kg/d or 150 mg/d	Anorexia, GI, rash	Possible interaction with Anisindione, Dicumarol.
N3 Fatty Acids		2000 mg tid	Eructations	May increase bleeding potential.
Feverfew	MIG-99	6.25 mg tid/3 mo	Arthralgias, oral ulcerations	Uterine contractions in pregnant women. Cross reactivity with daisy allergy.

(continued)

Table 11.1 (continued)

Nutraceutical	Preferred formulation	Dose/time	Side effects	Precautions, interactions, contraindications
Ginkgo	Migrasoll Pharmaval Srl	Ginkgolide B 80 mg, coenzyme Q10 20 mg, vitamin B2 1.6 mg, magnesium 300 mg	Atopic dermatitis, muscle weakness	May increase bleeding potential. Severe allergic reactions with crude ginkgo plant parts. Interacts with cytochrome P450 3A4 (CYP3A4) substrates and some HIV drugs.
Magnesium	Oral—varies IV—sulfate	400–1200 mg/d/3–4 months	GI	Caution in pts with renal failure. Decreased absorption of Gabapentin.
Melatonin		3 mg/1 h prior to bedtime/3 months	Lethargy, dry mouth, constipation, weight gain	Hypotension, hypoglycemia, caution in pts on opioids.
Petasites	Petadolex	50–150 mg/d	GI, cholestatic hepatitis, liver cancer	Not for use in children and pregnancy. Must be free of pyrrolizidine alkaloids.

United Kingdom's Medicines and Healthcare Products Regulatory Agency took all *Petasites* products off the market, citing safety concerns [19]. Other European regulatory agencies have similarly removed this product from the market, often for failure to adhere to stringently low levels of PA [11].

While Petadolex continues to be available in the US, patients should be advised of these potential risks [18]. It should not be recommended for use in children, pregnant or nursing women, or patients with kidney or liver disease [19, 20].

Magnesium—Level B Evidence

Intravenous magnesium supplementation is widely used for acute and prophylactic treatment of migraine, while oral administration is often used for prophylaxis. Magnesium is thought to decrease the sensitivity of the brain to external and internal stimuli, and as an *N*-methyl-D-aspartate (NMDA) receptor antagonist, magnesium is essential for synaptic plasticity and memory [19, 21, 22]. Magnesium

also serves to maintain vascular tone, promote propagation of cortical impulses, and regulate levels of inflammatory mediators, serotonin, nitrous oxide, and substance P [6].

Hypomagnesaemia is not uncommon and is seen in up to 15% of the general population [23]. Adult and pediatric migraneurs are often deficient in magnesium, as measured in the blood, saliva, or brain. Such deficiency is more commonly seen in migraine with aura (MA) and migraine during menses (MM) and is known to worsen during attacks [24–28]. Ionized serum magnesium (IMg^{2+}) is thought of as the most accurate reflection of aberrations of magnesium levels in the soft tissue, but the more commercially available red blood cell (RBC) magnesium is considered an acceptable substitute [29].

Acute Management

Mauskoup et al. demonstrated that 50% of subjects (n = 40) with migraine had low levels of IMg^{2+} during an acute migraine attack. 85% of these had a reduction in pain of more than 50% with IV infusion of magnesium sulfate ($MgSO_4$), and treatment response correlated with the level of magnesium deficiency [30]. A 2014 meta-analysis of existing studies looked at acute management 30 min after infusion of IV $MgSO_4$. There was no reduction in pain and no effect on need for rescue medications. Furthermore, an increase in adverse effects was also noted. The authors cited heterogeneity of studies and small sample size as confounding factors [31]. Due to methodological selection criteria, the Mauskoup trial was not included in this review.

Prevention

Most published trials examine magnesium for acute migraine management. Teigen and Boes performed an evidence-based review of 4 RCTs of magnesium supplementation for prophylaxis. While the studies consistently showed a relationship between migraines and lower magnesium status, there was significant variability in the effectiveness of treatment. The authors attribute this to methodological differences and confounding variables, including endpoints and formulations of magnesium used. They propose that magnesium levels should be assessed in migraine patients and that increased dietary magnesium intake could offer a reasonable alternative for prophylaxis [32].

Riboflavin—Level B Evidence

It has long been hypothesized that vitamin B_2 could be utilized in migraine treatment and prophylaxis. There is a known interictal reduction of phosphorylation

potential (OXPHOS) in migraine without aura (MO), MA, and MM which impacts mitochondrial energy production [33]. This results in hyper-excitability in both neurons and muscle fibers of migraneurs. Vitamin B_2 plays a role in OXPHOS reactions that can prevent this hyper-excitability and benefit mitochondrial energy production [30, 34]. Figure 11.1 outlines the possible roles for riboflavin in the prevention of headache.

The clinical trials of riboflavin in prevention of migraine attacks are mixed. While some show a significant improvement, others show no or minimal effects. The studies vary widely in terms of type of migraine, sex, age, dosages, length of time the product is used, placebo control and therapeutic end points. Sample sizes are generally small [34].

One of the most frequently cited RCTs noted a 50% reduction in attacks in 59% of adult patients taking 400 mg of riboflavin daily for 3 months [35]. A combination product of 400 mg of riboflavin, 300 mg magnesium and 100 mg of feverfew was compared to a "placebo" of 25 mg of riboflavin. There was a difference in both groups in the number of days with migraine and the frequency of attacks [36]. One recent study suggests that riboflavin is most effective in patients with the non-H mitochondrial DNA haplotype, which is more prevalent in Europeans and associated with lower mitochondrial function [37]. Vitamin B_2 has also shown usefulness when added to other pharmaceutical preventative therapies [38].

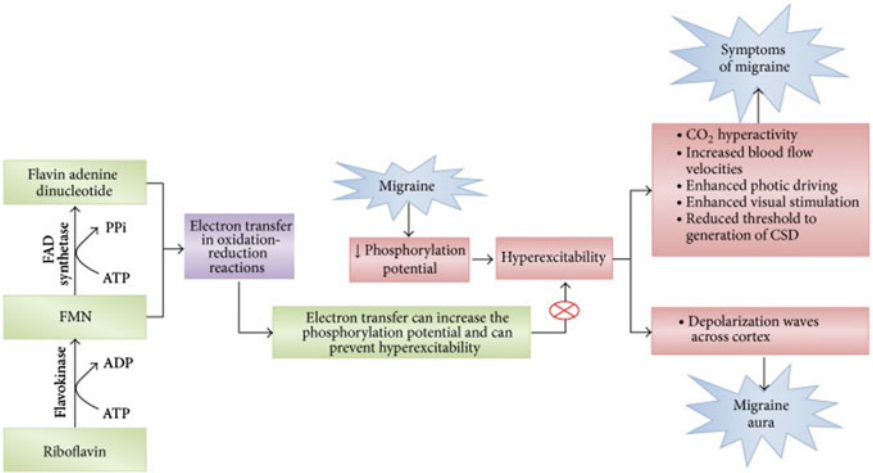

Fig. 11.1 Possible roles of riboflavin in ameliorating migraine. Schematic diagram depicting the possible roles of riboflavin in ameliorating migraine. *ATP* adenosine triphosphate, *ADP* adenosine diphosphate, *FAD* flavin adenine dinucleotide, *PPi* pyrophosphate (anion $P_2O_7^{4-}$), *CO_2* carbon dioxide, and *CSD* cortical spreading depression. *Red circled* times symbol: inhibition of the pathway (Reproduced from Shaik, M. M. and S. H. Gan (2015). "Vitamin supplementation as possible prophylactic treatment against migraine with aura and menstrual migraine." Biomed Res Int 2015: 469529 [34] under the Creative Commons Attribution License. http://www.hindawi.com/journals/bmri/2015/469529/)

Overall, because of the favorable risk benefit ratio, most would recommend including riboflavin in the treatment plan of adult migraneurs [19]. A recent systematic review of use in children has not shown efficacy, and therefore its use is not recommended for pediatric use at this time [39].

Feverfew—Level B Evidence

The plant *Tanacetum parthenium L* has a long history of traditional use in the prevention of migraine. It is unclear how feverfew works. Parthenolide, a sesquiterpene lactone found in the aerial portion of the plant, is widely held to be the most important active ingredient. Parthenolides most likely exert their effect by inhibiting prostaglandin production, interfering with both contraction and relaxation of intracerebral blood vessels. They may also affect the secretion of serotonin [40]. A Cochrane review of this herb was published in 2004 and updated in 2015. While many studies suggested benefit, they failed to show efficacy due to poor trial design with low numbers of patients and unstable extracts of the product [40–42].

MIG-99 is considered a superior formulation of feverfew. This supercritical CO_2 extraction enriches the parthenolide content and produces a chemically stable product. Clinical trials performed with its predecessor product are susceptible to variance in both concentration and stability of the parthenolides and clinical results are variable.

One of two studies utilizing MIG-99 demonstrated no benefit over placebo in 147 subjects over 3 different dosages of the product. It was, however, noted that a smaller subgroup of the most severely affected patients had a response to MIG-99 [43]. Therefore, a second RCT on a larger pool of subjects ($n = 170$) was performed. Here, a significant reduction in both frequency and severity of attacks was noted (30.3% vs. 17.3%). The effect of MIG-99 begins as early as one month and reaches maximal benefit in two months. Once usage is stopped, the effect is sustained for at least four months [44]. In both studies, adverse effects of MIG-99 were similar to placebo.

Coenzyme Q10 (CoQ10)—Level C Evidence

CoQ10 is an enzyme cofactor critical for maintenance of mitochondrial energy stores [19]. It has been shown to be deficient in approximately one-third of children and adolescents with migraine. This deficiency is potentially due to oxygen free radical formation during migraine attacks that could deplete stores of CoQ10. Supplementation in deficient children has shown a statistically significant reduction in both frequency and disability associated with attacks [45, 46].

In a group of patients treated with standard multidisciplinary treatments for migraine, addition of CoQ10 in a crossover RCT showed a difference in frequency of attacks only early on in therapy [46]. In adults, a small open label study showed

lowered migraine frequency with 3 months of 150 mg daily [47]. In another RCT ($n = 42$), 300 mg daily was noted to improve frequency of attacks, days with headache, and headache-associated nausea [48]. Side effects are minimal and noted in less than 1% of the subjects [47].

Melatonin—Level U Evidence

Melatonin acts as an anti-inflammatory by scavenging free radicals and down regulating pro-inflammatory cytokines. It is also involved in neurovascular regulation by affecting maintenance of nitric oxide, dopamine, and serotonin. Melatonin could also affect the circadian predilection for migraines noted in some patients. Altered melatonin levels are seen in various forms of migraine [49, 50]. *Petasites* and feverfew have substantial amounts of melatonin and are used in the treatment of migraine [11, 51].

The first study of use of melatonin for prevention of migraine showed efficacy, but was underpowered and open label [50]. A subsequent study using a prolonged release product did not show improvement in attack frequency when compared to placebo [52]. In a randomized, multicenter group design melatonin was slightly superior to 25 mg of amitriptyline in days per month with headache. Side effects were minimal and less than in the amitriptyline group [53].

Vitamins B6, 9, 12—Level U Evidence

Elevated homocysteine levels have been implicated in MA. It is thought that this deficiency produces an inflammatory reaction in the meninges and endothelial injury within cerebral blood vessels. Trigeminal fibers are activated and nitric oxide becomes less bioavailable [54]. A schematic of the role of vitamins B6, 9 and 12, in migraine pathophysiology is outlined in Fig. 11.2.

The enzyme methylenetetrahydrofolate reductase (MTHFR) is essential to re-methylation of methionine and elimination of homocysteine. This reaction requires vitamins B6 (pyridoxine), B12 (cobalamin) and B9 (folic acid). Hyperhomocysteinemia has been observed in deficiencies of these vitamins [34]. The MTHFR C677T genetic variant has been associated with increased levels of homocysteine and risk of MA [55].

Menon et al. demonstrated an inverse relationship between dietary intake of B9 and MA frequency in patients homozygous for MTHFR C677T [54]. Lea and colleagues demonstrated a reduction in migraine frequency, disability, and pain severity with a reduction in homocysteine achieved with a 6-month protocol of folic acid (2 mg), B6 (25 mg) and B12 (400 mcg) [56].

The selected vitamin content of foods is included in Table 11.2

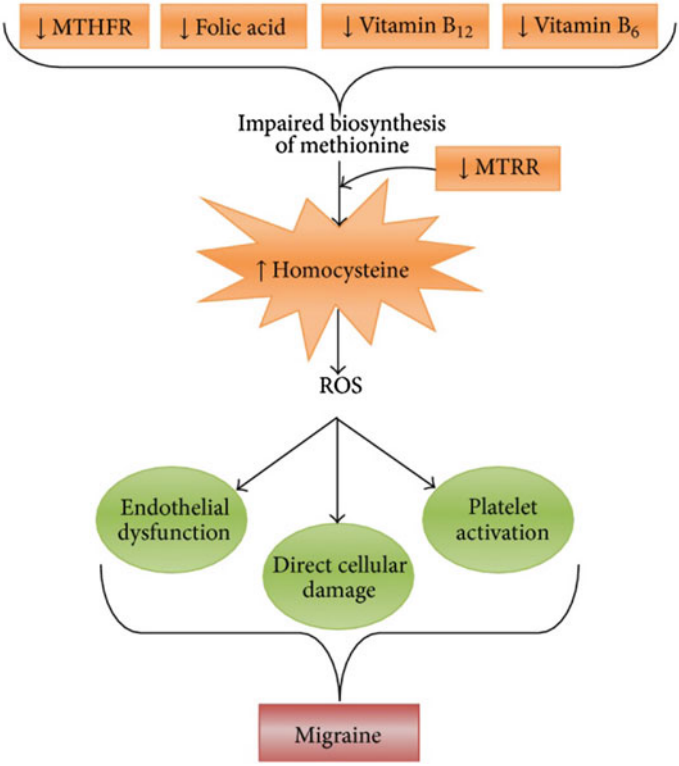

Fig. 11.2 The role of vitamins B6, B12, and folic acid in migraine pathophysiology. Schematic representation depicting the role of vitamins B6, B12, and folic acid in migraine pathophysiology. *MTRR* (or *MSR*) methionine synthase reductase, *MTHFR* methylene tetrahydrofolate reductase, and *ROS* reactive oxygen species (Reproduced from Shaik, M. M. and S. H. Gan (2015). "Vitamin supplementation as possible prophylactic treatment against migraine with aura and menstrual migraine." Biomed Res Int 2015: 469529 [34] under the Creative Commons Attribution License. http://www.hindawi.com/journals/bmri/2015/469529/)

Alpha Lipoic Acid (ALA)—Level U Evidence

Thioctic (alpha lipoic) acid is a water and fat soluble antioxidant, which like riboflavin and CoQ10 enhances mitochondrial metabolism and ATP production. It does so by removing reactive oxygen species and chelating transition metal ion byproducts of oxidative stress [57, 58].

In a RCT of 26 study patients, ALA (600 mg daily for 3 months) showed a reduced monthly attack frequency that was not statistically significant when compared to placebo. Within-group analyses showed a significant reduction in attack frequency, headache days, and headache severity in patients treated with ALA. These benefits were not seen in the placebo group. The authors conclude that the study group was underpowered, but that a clear trend toward less frequent attacks

Table 11.2 Selected vitamin content of foods

Vitamin or supplement	Foods containing
Omega 3 fatty acids	Salmon, tuna, mackerel, anchovies, sardines, herring
Magnesium	Legumes, almonds and other nuts, spinach, sweet potatoes, white potatoes, swiss chard, sunflower seeds, brown rice, whole grains, and dairy products
Alpha lipoic acid	Meat products, heart, liver and kidneys, broccoli, spinach, brewer's yeast, brussel sprouts, peas, tomatoes
Riboflavin	Milk, eggs, cheese, yogurt, broccoli, almonds, soy, fortified cereal
B9	Fortified foods, spinach, broccoli, lettuce, okra, asparagus, bananas, melons, lemons, legumes, yeast, mushrooms, organ meat, beef liver, kidney, orange and tomato juice
B12	Meat, fish, poultry, eggs, dairy
B6	Whole grain products, liver, bananas, green beans, carrots, chicken, eggs, meat, fish, spinach, walnuts and sunflower seeds

was noted. They also note that like riboflavin and CoQ10 results accrue over time. No side effects were noted [59].

In a randomized, uncontrolled study adolescent girls were given Topiramate or ALA alone or both combined, for one month. All three groups showed improvement in migraine frequency. Reduction in mean monthly migraine days was significantly greater in the group receiving combined Topiramate ALA therapy (from 12.32 ± 1.85 to 5.74 ± 1.1). Side effects were noted solely in the Topiramate monotherapy group [58].

Essential Fatty Acids—Level U Evidence

Omega-3 polyunsaturated fatty acids (n-3 FA) are known to affect production of inflammatory cytokines. N-3 fatty acids can also be converted to lipid mediators that have antinociceptive properties, such as endovanilloids, eicosanoids, endocannabinoids, and resolvins. In addition, these compounds have anti-coagulant and vaso-relaxant properties, all of which suggest their usefulness in the treatment of migraine [60, 61].

There is only one existing RCT of n-3 FAs for migraine. After a four week single blind placebo run in period, patients were assigned to 16 weeks of either 6 g of n-3 FA daily or placebo. There were no differences noted in the mean number of attacks during the last four weeks of the study but the overall number of attacks was reduced in the treatment group. A greater level of eructation was noted in the n-3 related group without other side effects [61].

Omega 6 polyunsaturated fatty acids (n-6 FA) are prevalent in the western diet. These are thought to potentially contribute to headache pathogenesis by hyperactive

metabolism of n-6 linoleic (n-6 LA) and arachidonic (n-6 AA) acids, and insufficient metabolism of n-3 eicosapentaenoic (n-3 EPA) and docosahexaenoic (n-3 DHA) acids [62]. Although not specific to migraine, Ramsden and colleagues treated a cohort of patients (n = 56) with chronic daily headaches with targeted dietary fatty acid alterations. The study was a randomized, single-blinded, parallel-group clinical trial with a four week pre-intervention phase. Patients were randomized to 12 weeks of dietary interventions: a high n-3 plus low n-6 (H3-L6) diet, or a low n-6 (L6) one. Clinical outcomes were tracked by a headache diary (HIT-6) during both phases of the study. Biochemical outcomes included assessments of bioactive n-3 and n-6 derivatives and erythrocyte n-6 in highly unsaturated fatty acids (HUFA) score. Results showed that both groups achieved targeted intakes of n-3 and n-6 fatty acids, but the H3-L6 intervention produced a significantly greater improvement in the HIT-6 score, number of headache days/month and number of headache hours/day.

In contrast to the negative results noted with supplementation of n-3 fatty acids alone, the authors conjecture that while n-3 ingestion is known to increase circulating EPA + DHA and to reduce AA and bioactive AA derivatives, the dietary n-6 lowering component may be necessary to produce maximal clinical benefit. By lowering n-6 fatty acids, n-3 fatty acids have less competition for hepatic desaturation and are thus more readily incorporated into tissue and converted to bioactive derivatives [60].

Ginkgolide B—Level U Evidence

Ginkgolide B, extracted from *ginkgo biloba* tree leaves, is a natural modulator of the action of glutamate in the CNS. Glutamate plays a role in initiating and propagating spreading depression seen in MA, through stimulation of glutamate receptors linked to NMDA channels [63]. It also is a potent inhibitor of platelet-activating factor (PAF), which is pro-inflammatory and nociceptive. Thus there has been interest in the use of Ginkgo for treatment of MA [63].

None of the existing clinical trials examining the use of Ginkgolide B for migraine are placebo controlled, and all utilize a combination product, Migrasoll (Pharmaval Srl) which contains Ginkgolide B 80 mg, CoQ10 20 mg, vitamin B_2 1.6 mg, and magnesium 300 mg. When administered twice daily for four months to 50 women suffering from MA, decreased frequency and duration of attacks was noted [63]. Similar results were produced in a more recent study of both men and women, and further substantiated in a larger group (n = 119) of pediatric migraine patients [64, 65]. While none of the studies found serious side effects, gingko should be used with caution in patients on blood thinners, as spontaneous bleeding is potentially a concern, though a meta-analysis of patients on ginkgo did not note any increase in bleeding potential over placebo [66].

Phytoestrogens—Level U Evidence

Phytoestrogens found in soy, such as genistein and daidzein have been reported to be helpful with menopausal symptoms. They are heterocyclic phenols and are structurally related to estradiol-17-beta and selective estrogen receptor modulators (SERMS). They exhibit weak mixed agonist/antagonist SERM activity. Black cohosh (*Cimicifuga racemosa*) is derived from the roots of a perennial plant from the buttercup family and has been found to contain several compounds with estrogen receptor activity similar to soy isoflavones. Dong quai (*Angelica polymorpha*) is a member of the plant family that includes parsley, celery, and carrots. Dong quai has been used for centuries in traditional Chinese, Korean, and Japanese medicine for relief of menopausal symptoms. Animal studies have shown it to have effects similar to estrogen [67].

In a group of 49 patients with MM, subjects were randomized to receive either placebo, or 60 mg soy isoflavones 100 mg dong quai, and 50 mg black cohosh daily for 24 weeks. Each component was standardized to its primary alkaloid. Average frequency of migraine attacks was reduced from 10.3 in placebo-treated patients to 4.7 ($P < 0.01$) in the treatment group. Migraine severity was also significantly diminished. The effect began after one month of treatment [67].

Cannabis—Level U Evidence

Cannabis is composed of more than 400 compounds, 60 of which are naturally occurring cannabinoids (CBs). These include psychoactive Δ^9-tetrahydrocannabinol (THC), and cannabidiol (CBD). The latter makes up 40% of the plant's extract and is one of the primary constituents of medical marijuana [68]. CBs have serotonergic, dopaminergic, and anti-inflammatory effects. They stimulate the endocannabinoid system found throughout the body comprised of specific cannabinoid receptors and endogenous cannabinoids. This system includes cannabinoid 1 (CB1) and 2 (CB2) receptors, and cannabinoid ligands such as Anandamide (AEA) and 2-arachidonoylglycerol (2-AG).

One of the most documented uses of medicinal marijuana is in the treatment of chronic pain, and it has long been argued that cannabis is ideally suited for use in treatment of migraine [69]. CBs are active through CB1 receptors in various areas of the brain and brainstem involved with migraine pathophysiology including the trigeminal nucleus and ganglia [70]. When these receptors are activated they can inhibit dural trigeminovascular nociceptive responses [68]. THC inhibits serotonin release from platelets during migraine, stimulates 5-HT synthesis, and modulates dopamine production [71]. The endocannabinoid AEA modulates pain signaling in the central nervous system in various ways by inhibiting dural blood vessel dilation and via indirect effects on NMDA, opiate, and γ-aminobutyric acid (GABA) receptors [71].

There are five case reports in the literature of patients who used illicit marijuana products for treatment of their vascular or migraine headaches and who experienced an overall decrease in migraine headache [72]. There is also one retrospective observational chart review of patients treated at a medical marijuana clinic. Of 121 patients with a primary diagnosis of migraine, 85% reported decreased headache frequency with the use of medical marijuana. Most patients used more than one form of marijuana and used it daily for prevention and acute treatment. Formulations included vaporized, topical, edible, and smoked. Approximately one half of patients used prescribed migraine medications concomitantly. Somnolence was the most common side effect. Unfortunately, there were no standardized methods of evaluating efficacy since the treatment responses were based upon the medical record and subjective reports [68].

As medical marijuana becomes more readily available it is possible that we will see further research that supports or refutes its use in the treatment of migraine.

Niacin-Level U Evidence

When taken intravenously or orally, niacin produces cutaneous flushing that might produce intracranial vasodilation and prevent the vasoconstriction associated with MA. The scientific evidence is stronger for niacin's peripheral vasodilatory effects, and the central mechanisms of niacin in acute MA remain unclear. Prophylactically, niacin helps maintain mitochondrial energy metabolism by increasing substrate availability to complex I [73]. While the literature suggests oral, sustained release (SR) or IV niacin could be helpful for prevention and acute treatment, all of the existing trials are small case series and none have placebo controls [73, 74].

Diet and Exercise

Diet–Level U Evidence

Food allergies, metabolic abnormalities and specific "trigger" foods such as chocolate, red wine, cheese, and processed meats have been examined for their potential to precipitate migraine. Some commonly reported food and chemical triggers are included in Table 11.3. Overall, there are no studies that clearly show an unequivocal relationship between specific dietary intake and migraine [75]. Caffeine, while utilized in a number of migraine medications, has been suspected as causing headaches in both adults and children with overuse (>200 mg/d). It is generally recommended to keep consumption less than this level, and not to stop abruptly as withdrawal has been clearly shown to precipitate headaches, and is potentially also a precipitant of migraine [76]. Low fat, vegan, and elimination diets

Table 11.3 Potential trigger foods [76]

Food or chemical	Present in	Strength of evidence	Possible mechanism
Aspartame	Sugar substituted foods	Moderate	Increased phenylalanine.
Caffeine/theobromine consumption	Coffee, tea, chocolate, colas	Moderate	Modulation of noradrenergic and nocioceptive pathways. Enhanced sympathetic tone, serotonin and dopamine.
Caffeine withdrawal		Strong	Increased blood flow in posterior cerebellar and basilar artery.
Chocolate		Weak	Based on components phenylethylamine, theobromine and caffeine.
Histamine	Cheese, fish, sausage, vegetables, and alcoholic beverages	Moderate	NO_2 release.
MSG	Frozen, canned or dried foods, processed meats, international and snack foods, tomato or barbecue sauces	Moderate	Vasoconstriction. NMDA receptor agonist. Release of NO_2.
Nitrates	Cured meats, cabbage, carrots, celery, lettuce, radishes, beets, spinach	Moderate	NO_2 release.
Polyphenols	Red wine, some vegetables and spices	Weak	Serotonin release.
Phenylethylamine	Chocolate, some mood and weight loss supplements	Weak	Alterations in cerebral blood flow. Release of norepinephrine.
Sulfites	Beer, wine, vinegar, dried fruit, grape juice	Weak	Release of histamine. Production of sulfur dioxide causing irritation of cholinergic neurons.
Tyramine	Cheese, wine, beer, preserved fish and meats, sauerkraut, yeasts	Weak	Release of norepinephrine. Dopamine synthesis.
Wine		Moderate	Based on components: tyramine, sulfites, histamine, polyphenols.

Table 11.4 Elimination diet as per Bunner 2014 [77]

	Avoid these foods	Favor these foods
Grains	Wheat, rye, barley, corn	Oats, rice, quinoa, buckwheat, amaranth, sorghum, millet, teff
Fruits	Citrus, bananas, apples	Pears, apricots, blueberries, plums
Vegetables	Night shades (tomatoes, eggplant, peppers, potatoes), onions, garlic, sweet potatoes, yams, celery	Artichokes, asparagus, broccoli, cauliflower, brussel sprouts, cabbage, bok choy, carrots, chard, kale, collard and mustard greens, spinach, lettuce, zucchini
Legumes	Soybeans, chickpeas, peanuts	Lentils
Other	Animal products, nuts, seeds, chocolate, sugar, coffee, tea, alcohol	Olive oil, vanilla extract, brown rice syrup, maple syrup, salt

have been associated with improvement in headache pain [77–80]. An elimination diet used by Bunner et al. is outlined in Table 11.4 [77].

There is good data to suggest that for some patients, fasting can precipitate an attack [81]. There are many potential mechanisms for this, including alterations in levels of serotonin and norepinephrine, release of stress hormones that could induce headache; induction of hypoglycemia and withdrawal of caffeine or nicotine. It is suggested that all migraineurs avoid prolonged periods of fasting [76].

In a population-based retrospective of a 326 migraine-patient database, no dietary factors were identified as causing an increase in risk of migraine attacks. However, when the same database was examined at the individual level, dietary factors were significantly associated with attacks in some patients although individual dietary triggers were seen in less than 10% of patients [82, 83]. Overall, the data suggests that although many foods and substances are often cited as headache triggers by patients, not all of the foods will trigger a migraine in any one individual.

These findings are not surprising. Specific dietary triggers first need to be absorbed through the GI tract, undergo appropriate degradation in order to enter the vascular space, and cross the blood–brain barrier to be able to access appropriate cerebrovascular or neuronal receptors and have an effect. The trigger must be of sufficient quantity and have appropriate affinity for the receptor. Other cofactors may be required for the trigger to precipitate migraine, or multiple triggers may need to be present. Any of these dynamics could vary from person to person and from exposure to exposure [76, 78]. Therefore dietary approaches must be specifically individualized for the patient.

Multiple studies show a relationship between migraine and obesity. The reasons for this are not well understood, but one possible explanation is shared inflammatory processes. It is possible that obesity promotes a low-grade chronic inflammatory state, which may exacerbate the already existent neurovascular inflammatory response in migraine. There could also be common behavioral risk factors that promote further inflammation, one being poor dietary habits [75]. In addition, obesity has also been linked to sleep apnea, snoring, and insulin resistance, which are also associated with migraine [84].

Exercise–Level B Evidence

The exact mechanism by which exercise affects headache is unclear, although various hypotheses have been suggested. These include improved cardiovascular, cerebrovascular, and psychological states, as well as neurochemical changes such as sustained higher serotonin levels, and activation of endogenous endorphins, opioids, and cannabinoids. Both hyper and hypo-functioning of the sympathetic and parasympathetic nervous systems have been reported as well as improved responses to stress, anxiety, and depression [85, 86].

There have been recent randomized trials that provide level 1 evidence that exercise can help prevent migraine occurrence. Most existing studies utilize aerobic exercise performed at the submaximal level (50–85% VO_2 max or 50–85% of maximal heart rate or 11–16 on the Borg Ratio Scale of perceived exertion) for the purpose of cardiorespiratory fitness [86]. Reasons for choosing this form of exercise include less risk of precipitating cardiovascular events and exercise induced migraine. Warm up and cool down should be incorporated for similar reasons [87]. This level of activity also coincides with the American College of Sports Medicine recommendations for regular aerobic exercise, and would be appropriate at the lower levels for more unfit patients. In a cross-sectional study of medical students with migraine, there was no difference between aerobic exercise and strength training with regards to impact on migraine [86, 88], Kiko exercises, similar to Chinese Qi Gong, have also shown efficacy [86].

Neck pain is a common accompaniment of migraines, and is reported more frequently than nausea [89]. Isometric neck strengthening exercises can be useful in these cases, as they eliminate muscle spasm and strengthen the musculature. Mauskopf recommended a simple exercise repeated 10–15 times throughout the day for 2 weeks for improvement. See Table 11.5 for an outline of recommended exercises [90].

Manual Therapy

Manual therapy is a broad category of alternative medicine that includes acupuncture, chiropractic therapy, physiotherapy, massage, and trigger point injections and release. It may also involve correction of posture, stretching,

Table 11.5 Neck exercises [90]

1	Place hand on one side of head
2	Keep head stationary and in a neutral position
3	Apply sustained pressure for 10–15 s
4	Repeat on the other side of head, forehead and then occiput
5	Do this exercise 10–15 times daily for 2 weeks

mobilization, and manipulation techniques. Given the frequency with which these therapies are used, the AAN published a guideline incorporating a robust review of the literature regarding the use and efficacy of non-pharmacologic therapy, although it has not been updated since 2000 [10]. According to the AAN, patients who may benefit the most from behavioral treatments include those who have a preference for non-pharmacologic treatments; have an intolerance or medical contraindication to pharmacologic treatments; have had minimal or no response to pharmacologic treatments; are pregnant or nursing; have used or are currently using analgesics or other medications that may aggravate headache or reduce the effectiveness of headache medications; have life stressors or have inadequate coping mechanisms for stress. In addition to the AAN, various other reviews that have been conducted on these treatments in more recent years have provided a substantial body of literature supporting the use of non-pharmacologic therapy in migraine prophylaxis.

Acupuncture—Level A Evidence

Among the multiple forms of manual therapy, acupuncture is very frequently cited in the treatment of migraine. It typically involves insertion of thin needles into specific points in the body, known as meridians. Acupuncture has been shown to be effective for various types of pain relief, including headache and osteoarthritis, according to several Cochrane reviews [91–95].

The most recent Cochrane review studying the use of acupuncture in migraine prophylaxis was published in 2009 [93]. This review included 22 trials and showed that acupuncture is at least as effective as prophylactic pharmacologic treatment. Interestingly, the 14 trials that compared "true" acupuncture with sham interventions showed no significant difference in efficacy. A systematic review of studies on the effectiveness of placebos in migraine prophylaxis has even shown that compared to their respective interventions, sham acupuncture was associated with higher responder rates compared to responder rates for oral pharmacological placebos [96].

As such, it is still unclear how acupuncture alleviates migraine symptoms. In a study comparing 12 patients with MO and 12 control patients without migraines, acupuncture was associated with normalizing effects on functional MRI (fMRI) [97]. Patients with migraines had fMRIs completed both before and after they received 4 weeks of acupuncture treatment. Pretreatment fMRIs showed that functional connectivity in the right frontoparietal network, the left precentral gyrus, the left supramarginal gyrus, the left inferior parietal lobule, and the left postcentral gyrus was significantly decreased compared to the fMRIs of control patients.

In an era in which the price of health care is under great scrutiny and debate, exploration of cost effective non-pharmacological interventions is even more relevant. In fact, a study of 401 patients with chronic headache, primarily migraine, in England and Wales showed that acupuncture was a cost-effective treatment [98]. While multiple studies comparing acupuncture with pharmacologic therapy have not systematically shown that acupuncture was more effective in decreasing such

measures as frequency of migraine attacks and pain intensity, they have found that acupuncture is equally as effective as pharmacologic therapy with fewer side effects and complications, and higher compliance rates [99–102].

Chiropractic Therapies and Massage—Level C Evidence

Chiropractic therapies, including spinal manipulation, have also been used widely for the treatment of various disorders and very commonly for pain. Chiropractic spinal manipulation is a treatment utilizing high-velocity, low-amplitude movements directed at a specific joint. Several studies on chiropractic spinal manipulation showed improvement in migraine patients based on migraine attack duration, migraine frequency, and use of rescue medications [103–105]. However, some studies did not have adequate control groups. Likewise, studies on the use of massage therapy showed significant improvement after treatment compared to controls but had low sample size and lacked data such as duration of migraines [106, 107].

Trigger Point Injections and Release—Level C Evidence

Headaches have also been associated with trigger points, which are areas of sustained muscular contractions causing pain [108]. Various methods have been utilized to release these muscular contractions and alleviate pain, including massage, injections of local anesthetic such as ropivacaine, and greater occipital nerve blocks using local anesthetic with or without corticosteroids. While studies have shown these therapies to be useful in tension-type headache, there is less evidence in the literature supporting their use in migraines. There has been one recent prospective study of trigger point injection showing up to 59% improvement in migraine [109]. However, RCTs are lacking. Furthermore, multiple RCTs of greater occipital nerve block have had conflicting results regarding the efficacy of this therapy in migraine headache [110, 111]. Given that this therapy is often used for headache disorders, more research into its efficacy would provide further insight into its use.

Mind/Body Techniques

Relaxation Training—Level A Evidence

A review of the literature published in 2007 found multiple studies to support the use of mind–body therapies, including relaxation, to be efficacious for migraine treatment [112]. In addition, the AAN found 10 trials comparing relaxation techniques, principally including progressive muscle relaxation, autogenic training, and

meditation or passive relaxation [10]. Averaging the results of these studies showed a 32% improvement in headache index or frequency of headaches.

Biofeedback—Level A Evidence

Biofeedback is also a commonly used therapy for migraine and provides methods by which a patient receives physiologic data in order to consciously control a function or symptoms that are typically automatically regulated. The most common biofeedback therapies used for migraine are thermal feedback, blood-volume-pulse feedback, and electromyographic feedback. Based on the review by the AAN, effective non-pharmacologic treatments recommended for migraine prevention include relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy [10]. Multiple subsequent reviews have found that biofeedback was an efficacious treatment option for migraine prophylaxis [113, 114].

Cognitive-Behavioral Therapy (CBT)—Level A Evidence

CBT, or stress-management therapy, is also used in migraine management. In the analysis performed by the AAN, an average of the results of 5 trials found that CBT had an average effect size of 0.54 [10]. Additionally, there has been one RCT on hypnotherapy [115]. Migraine frequency was significantly lower in the group receiving hypnotherapy, but this study had a small sample size of 47 patients and compared hypnotherapy to prochlorperazine, a drug infrequently used today. No confirmatory studies of hypnotherapy have been conducted since.

Other Modalities

Hyperbaric Oxygen Therapy—Level C Evidence

A less commonly used non-pharmacological therapy used for migraine treatment is hyperbaric oxygen therapy. Mechanisms for this treatment option include vasoconstriction and facilitating certain metabolic reactions in the brain that require oxygen. A Cochrane review recently included 3 trials with a total of 58 patients comparing hyperbaric oxygen therapy to sham for acute migraine [116]. This study showed that hyperbaric oxygen therapy was effective in relieving migraine headaches in the acute period but had no effect in preventing further attacks or for reducing the need for rescue medication. Furthermore, the level of evidence was low with missing data and small crossover studies. Although there was some

evidence for the effectiveness of hyperbaric oxygen therapy, further studies are needed, especially as it is costly and not widely available.

Summary

The widespread incidence of migraine headache has led to a plethora of potential therapies for relief from acute symptoms and for prevention. Allopathic medical management consists of conventional medications and control of concomitant illnesses. For many patients this does not decrease the burden of disease. A treatment plan that incorporates evidence based alternative therapies within an integrative framework can offer relief not found with conventional treatments alone.

Recommendations

The importance of performing a good medical history and physical exam cannot be overemphasized. Specific attention should be paid to circumstances surrounding occurrence of headaches, including frequency, triggers, related stress, and musculoskeletal factors. Success or failure of previous treatments should be taken into account. It may be necessary to screen for specific nutrient abnormalities such as magnesium, B12, and homocysteine, and to consider genetic typing for mitochondrial DNA and single nucleotide polymorphisms. The therapeutic approach to migraine needs to be individualized to each patient's needs.

Acupuncture, exercise, relaxation training, biofeedback and cognitive-behavioral therapy offer patients alternatives to conventional treatments and have good evidence of efficacy with a low profile of side effects. Consider supplementing with magnesium, MIG-99, riboflavin, or CoQ10, or minimally increasing their dietary sources, along with B6, 9, 12 and possibly n-3 FAs and ALA. Including a vegetarian diet low in n-6 FA's and avoiding identified patient-specific trigger foods can be useful for some. If a patient is peri or post menopausal, phytoestrogens might be helpful. If there is a nocturnal predilection for headache, melatonin or melatonin-rich nutraceuticals should be considered. In subjects who have a musculoskeletal component to their pain, perhaps refer for a trial of massage, trigger point therapy, and possible chiropractic intervention. Patients should be encouraged to incorporate neck exercises if neck pain is a commonly encountered symptom or prodrome.

If all treatment options have been exhausted, use of Petadolex or hyperbaric oxygen therapy should be discussed in detail with patients, as both have good evidence of efficacy. Patients should be guided through the risk benefit analysis of the use of these or any other integrative therapies chosen. Carefully monitoring patients through any elected treatment is prudent and will lead to the best patient care with the least untoward effects. When in doubt, consult reputable individuals in your area who have advanced training in integrative medicine, or in the specific therapies chosen.

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Appendix

About Migraine Disorders

Migraine Disorders is a broad term for a complicated neurological condition that includes different types of headaches. The hallmark migraine headache is an intense pain, lasting 4-72 hours, with associated nausea and light or noise sensitivity. Headaches may or may not be accompanied by temporary auras such as zigzagging lines, bright spots or visual loss.

Less well known, migraine disease may include many other parts of the nervous system. Therefore, some migraine sufferers experience multiple symptoms - some without pain. These include some forms of balance disorders, recurring sinusitis, burning tongue, abnormal smells, poor concentration, tinnitus, sleep disorders, mood disorders, abdominal complaints, pelvic floor pain, fibromyalgia, post-concussion headaches and more.

These conditions all share a common problem of an overly sensitive nervous system.

About 80% of migraine sufferers inherit their condition, but migraine disease varies significantly between sufferers. The disease also changes through a lifetime. It might start with abdominal pain and carsickness in childhood and end with chronic ear pressure and skin sensitivity in old age. About 20% of migraine sufferers develop almost daily pain. Due to hormonal influence, there are three women migraineurs for every male.

Treatments

- Set realistic goals. Expect to reduce the intensity and frequency of symptoms.
- Treatments involve trial and error. To track the effect, keep a daily diary.

Preventive treatment - lifestyle changes

The goal is to reduce the triggers that start migraines.

Reduce stress: Stress can be generated by intense exercise, dehydration, missed meals and too little or too much sleep. Work on maintaining routines. Seek professional help with cognitive behavior therapy (CBT), thermal and EMG biofeedback, relaxation training, physiotherapy and other complementary therapies.

Diet: There are many potential food triggers for migraine. Comprehensive lists of foods that may contribute to triggering migraine can be found on online. How and why people react to different food proteins or chemicals is not yet well understood. But it is worth trying to identify if you have a food trigger and then avoid it.

In general, food triggers fall into three main categories:

- Byproducts of food aging and fermentation: red wine, aged cheeses, yeast and yogurt
- Foods with ingredients that affect our nervous system: coffee, chocolate, MSG, aspartame, citrus fruits and the nitrates used as preservatives in many prepackaged foods, particularly cured meats
- Foods to which we have mild, or silent, allergies or sensitivities: major protein groups, such as milk, corn, soy and wheat (gluten). Gluten sensitivity is particularly a common issue with migraine sufferers.

While it is possible to have a blood test for food allergy, this method does not identify if a food is a trigger. Instead, the use of an elimination diet— a careful removal of specific foods over a specific time period, followed by a reintroduction of the food—is one of the most reliable methods to identify a dietary migraine trigger.

Rescue Medicines

Non-steroidal anti-inflammatory drugs (NSAIDs): Overuse may cause "rebound" headaches.

Aspirin	600-900mg
Ibuprofen (Motrin)	400-800mg
Naproxen (Aleve, Naprosyn, Anaprox)	500-1000mg
Flurbiprofen	100-300mg
Diclofenic sodium	50-100mg
Tolfenamic acid	200mg
Ketoprofen	50-75mg
Indomethacin (Indocin)	25-50mg
Piroxicam	20mg
Celecoxib (Celebrex)	100-200mg

Triptans: Sumatriptan (Imitrex ®,Treximet®), rizatriptan (Maxalt®), zolmitriptan (Zomig®), frovatriptan (Frova®), almotriptan (Axert®)

Anti-nausea medicines: Phenergan, Compazine, Reglan, Tigan, Zofran

Ergotamine/Dihydroergotamine – tablets, inhaler, nasal spray, suppository

Preventative Medicines: Supplements

For patients with more frequent symptoms, it is better to use a daily medicine to reduce the frequency and intensity of the symptoms. Here are the supplements that have the best evidence of effectiveness.

Magnesium: 200-1200 mg daily (common: 400-500mg). The higher the dose, the more likely it will reduce migraine symptoms. The major side effect is diarrhea (lower risk by dividing dose over day). Can lower blood pressure and interact with some heart medications, diuretic, antibiotics (aminoglycosides) and muscle relaxants.

Vitamin B2 (riboflavin): 500 mg daily. Will turn urine bright yellow. Can interact with TCI, anticholinergics, phenobarbital and probenecid. Found in milk, meat, eggs, nuts, enriched flour and green vegetables.

Feverfew: 6.25 mg three times daily. Avoid during pregnancy, combining with aspirin. May cause mouth sores. Watch for ragweed cross-sensitivity.

M.E. Mehle (ed.), *Sinus Headache, Migraine, and the Otolaryngologist*,
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Supplements available in combination products:

	cost per capsule	riboflavin	magnesium	coQ10	butterbur
Migravent	$ .67 (0.33)	300 mg (150)	300 mg (150)	300 mg (150)	50 mg (25)
Migraine Formula	$ .33	100 mg	62 mg	47 mg	18 mg
Headache Free	$ .36	200 mg	200 mg		
Mig Relief	$ .33	200 mg	180 mg		

Preventative Medicines: Prescription

Often used in low doses to minimize side effects:

Diprovalate/Divalproex: (weight gain, hair loss, avoid in pregnancy)
Topiramate: (weight loss, cognitive problems, kidney stones, avoid in pregnancy),
Propanolol, timolol or metoprolol: (fatigue, sexual dysfunction, hypotension, avoid if reactive airway)
Amitriptyline: (dry mouth, weight gain, sedation),
Venlafaxine: (agitation),
Atenolol: (fatigue, sexual dysfunction, hypotension),
Lisinoprit: (cough)

Other Preventative Therapies

Botox injections: Few side effects (10% neck pain, May need pre-authorization.)

Neuromodulation (Neurostimulation):
non-invasive: Cephaly, Spring TMS (eNeura), vagus nerve stimulation (GammaCore)

Invasive: sphenopalatine ganglion stimulation

Do You Have...

- pressure or pain across your cheeks, behind your eyes or across your forehead?
- a feeling your ears are blocked or under pressure, or have water in them?
- very sensitive ears; bothered by wind?
- dizziness or unsteadiness?
- motion intolerance like difficulty reading in a car or tolerating an amusement ride?
- light or sound sensitivity?
- unpleasant smells or taste?
- burning or tingling of the tongue?
- nasal congestion?
- runny nose?
- difficulty understanding what is said?
- dental or TMJ pain?

Even if you've never suffered from regular headaches, it's possible that you're among the 36 million Americans who suffer from migraine disease if you experience some of the symptoms above.

ASSOCIATION OF MIGRAINE DISORDERS

migrainedisorders.org

The mission of the Association of Migraine Disorders is to end the suffering from migraine illness through collaboration, education, research and support.

2015

ASSOCIATION OF MIGRAINE DISORDERS

Options for Treating Your Migraine

Migraine Medication Guide
INTERVENTIONAL MEDICINES
Dosing is intended for adults.

NSAIDs

Recommended for mild symptoms - use single dose

aspirin	600-900 mg
piroxicam (Feldene)	20 mg
ibuprofen (Motrin)	400-800 mg
naproxen (Aleve, Naprosyn)	500-1000 mg
flurbiprofen	100-300 mg
diclofenac sodium (Cambia)*	50-100 mg
tolfenamic acid	200 mg
ketoprofen	50-75 mg
ketorolac nasal spray	one 15.75 mg spray each nostril q6-8 h
indomethacin (Indocin)	25-50 mg 50 mg supp (compound)
celecoxib (Celebrex)	100-200 mg

ACETAMINOPHEN/ASPIRIN/CAFFEINE

Excedrin/Excedrin Migraine: 2 caplets once a day

TRIPTANS*†

Recommended for moderate symptoms.If nauseated, add anti-nausea drugs. For more severe symptoms, add NSAID.

almotriptan	Axert	tab	12.5 mg
eletriptan	Relpax	tab	20/40 mg
frovatriptan	Frova	tab	2.5 mg
naratriptan	Amerge	tab	1/2.5 mg
rizatriptan	Maxalt	tab	5/ 0 mg
	Maxalt MLT	melt	5/10 mg
sumatriptan	Imitrex	tab	25/50/100 mg
		spray	5/20 mg
		sc	4/6 mg
w/naproxen	Treximet	tab	85/500 mg
zolmitriptan	Zomig	tab	2.5/5 mg
	Zomig MLT	melt	5 mg

Caution: vascular disease (cardiovascular, cerebrovascular, peripheral) and pregnancy.

Drug interactions: SSRI, St Johns wort, MAOI, Propanolol (rizatriptan), CYP 3A4 inhibitors (itraconazole, nefazodone, ketaconazole), HIV protease inhibitors (ritinavir, indinavir, nelfinavir), CYP 1A2 inhibitors (cimetidine, ciprofloxacin)

Common side effects: dizziness, nausea, paresthesia, somnolence, pain/pressure/headache - slight different between agents.

Migraine Medication Guide
INTERVENTIONAL MEDICINES
Dosing is intended for adults.

ANTI-NAUSEA MEDS

anti-emetic and anti-headache effects; increase absorption of triptans, side effects: akathesia and dystonia.

promethazine (Phenergan) 25-50 mg suppositories or pill q6; 10 mg im
prochlorperazine (Compazine) 25 mg pills q4, 5-10 mg iv/im (not in kids)
metroclorimide (Reglan) 10-20 mg pills q4 or suppositories. 5-10 mg iv/im (max 30mg/d)
trimethobenzamide (Tigan) 200 mg tabs, suppositories or lozenges best for children
ondansetron (Zofran) 4-8 mg q6-8, least side effects; no sedation
chlorpromazine 12.5-37.5 mg iv, 25-75 mg im
domperidone 10 mg pill q8, 30 mg suppository, 10-20 mg iv

ERGOT ALKALOIDS †

dihydroergotamine (Migranal Nasal) 1 spray each nostril, q15 min, max: 4 sprays, avoid w/ triptan
ergotamine 1 mg/caffeine 100 mg tablet (Cafergot), 1-2 tabs q30 min - max 6 tabs
ergotamine 2 mg/caffeine 100 mg suppository, 1 sup pr q1 hr - max 2 sups

ACETAMINOPHEN / ISOMETHEPTENE / DICHLORALPHENAZONE

Amidrine, Duradrin, Michlor and others: may or may not be available but not FDA approved, Midrin: 2 caps, then 1 cap q1 hr, max 5 per 12 hrs

BARBITURATES †

high risk of dependency, overuse and abuse

butalbital 50 mg/acetaminophen 325 mg/caffeine 40 mg
butalbital 50 mg/acetaminophen 325 mg
butalbital 50 mg/aspirin 325 mg/caffeine 40 mg

Urgent Care Rescue Options

Sumatriptan 4 mg or 6 mg SC
Phenergan (promethazine) 10 mg iv/im
Compazine (prochlorperazine) 10 mg iv/im (not in kids)
Reglan (metrocloromide) 10 mg iv/im (max 30 mg/d)
DHE 4 mg nasal spray, 1 mg sc/im
Valproic acid – 500-1000 mg in 100-250 cc saline over 60 min
Magnesium sulfate 1 gm in 10% solution over 15 min
Occipital nerve block

Caution: To avoid rebound headaches, do not use any of these medicines more than **15 days per month** *for three months.*
† *To avoid rebound headaches, don't use more than* **10 days a month.**
**Approved by the Food and Drug Administration (FDA)*

Migraine Medication Guide
PREVENTATIVE MEDICINES
Dosing is intended for adults.

Migraine Prophylaxis: level A

divalproex/sodium valproate*	400-1000 mg /day
metoprolol	47.5-200 mg/day
propanolol*	120-240 mg/day
timolol*	10-15 mg/day
topiramate (Topamax)*	25-200 mg/day

divalproex sodium: (Depakote® ER—500-1500 nightly)
valproic acid (Depakene)/sodium valproate (Epilim):
250-500 mg bid.
Alternative for patients with cardiovascular diseases, seizures or bipolar disease

Mild/transient side effects: nausea, diarrhea, vomiting, weakness, fatigue, sleepiness, dizziness, hair loss, tremor, weight gain.
Serious side effects: pancreatitis, hepatitis. Monitor liver function and platelets.
Pregnant women, or any woman of childbearing potential: risk of neural tube defects

beta-blockers: fatigue, sexual dysfunction, hypotension

topiramate: weight loss, cognitive problems, kidney stones, pregnancy category D

* Approved by the Food and Drug Administration (FDA)

ASSOCIATION OF MIGRAINE DISORDERS
www.migrainedisorders.org
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Migraine Medication Guide
PREVENTATIVE MEDICINES
Dosing is intended for adults.

Migraine Prophylaxis: level B

riboflavin (vitamin B2)	400 mg/day
magnesium *trimagnesium dicitrate*	500-600 mg/day
feverfew	50-300 mg q12
feverfew CO2 extract	2.08-18.75 mg q8
amitriptyline	25-150 mg/day ***(see below)***
atenolol	100 mg/day (50-200 mg)
venlafaxine ER	150 mg/day (37.5-150 mg)
lisinopril	10 mg day
histamine	1-10 mg subc 2x week
fenoprofen	200 - 600 mg/day
ibuprofen	200 mg q12
ketoprofen	50 mg q8
naproxen (Aleve and others)	500 - 1000 mg/day
naproxen sodium	550 mg q12

amitriptyline: may start at 10mg
Advantage: helps with some sleep disturbances, can combine with propanolol.
Disadvantage: weight gain.
Use cautiously if patient has a history of seizures, difficulty urinating, glaucoma or increased intraocular pressure.
Avoid in children, during pregnancy and nursing.

Avoid if taking any MAO inhibitor, during or within five weeks of fluoxetine. May block guanethidine. Tricyclics potentiate alcohol, barbiturates, other CNS depressants. Delirium may occur with disulfiram, ethchlorvynol, paralytic ileus with anticholinergics and hyperpyrexia with anticholinergics, sympathomimetics. Monitor serum levels with CYP450 inhibitors (e.g., quinidine, cimetidine, phenothiazines, propafenone, flecainide, others)

adapted from:
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Lainez MJA et al. Optimal management of severe nausea & vomiting in migraine: Improving patient outcome. Patient Relat Outcome MEas. 2013; 4: 61-83
Robertson CE. Management of Migraine Headache in the Emergency Department. Semin Neurol. 2010;30(2):201-211

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Note: Page numbers followed by *f* and *t* indicate figures and tables, respectively

M.E. Mehle (ed.), *Sinus Headache, Migraine, and the Otolaryngologist*,
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