Integrative Headache Medicine

An Evidence-Based Guide for Clinicians

Lauren R. Natbony
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Editors

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Preface

Clinicians specializing in headache and pain medicine have long recognized that the treatment of chronic pain requires the coordinated actions of experts in multiple disciplines, including neurologists, pain physicians, behavioral psychologists, psychiatrists, physical therapists, social workers, and nutritionists. The combination of conventional and complementary medical services – integrative medicine – leads to improved patient satisfaction, reduced stress, and more readily treatable, less serious illness.

Patients understandably want to be engaged in their medical care and to gain an understanding of the problem and plan of treatment. They want to deal proactively with their healthcare and, at the same time, want physicians to address the full range of physical, emotional, mental, social, and environmental influences that affect their health. Through individualizing care, integrative medicine goes beyond the treatment of symptoms to address the multiple factors contributing to a patient's illness.

This book provides evidence-based approaches for using traditional medical therapies in conjunction with alternative approaches to optimize results. Our goal is to inspire clinicians to formulate personalized treatment plans, working together by integrating their expertise in a multidisciplinary context to address patients' unique conditions, needs, circumstances, and treatment.

The 12 chapters of this book present research and analysis relevant to the application of a broad array of non-pharmacological interventions in headache care. Chapter 1 provides an overview of integrative medicine and proposes a step-wise approach for incorporating integrative modalities into a headache practice. Chapter 2 focuses on the attention to be paid to relevant aspects of a patient's medical history, emphasizing that correct diagnosis is the key in providing a comprehensive treatment and healing strategy. It then reviews conventional medical assessments to rule out secondary causes of headache. The next four chapters deal with lifestyle factors that play a role in headache, including trigger identification, exercise, nutrition, and sleep. The scope of mind-body therapies such as acupuncture, yoga, and mindfulness is explored in Chap. 7, and the psychology of pain is the subject of Chap. 8. An emphasis is placed on the need for a collaborative diagnostic and treatment approach among psychiatrist, psychologist, and neurologist in treating patients

with co-morbid mood disorders. Chapter 9 investigates the safety and efficacy of nutraceuticals, or pharmaceutical alternatives, and makes pointed recommendations regarding their use. The final three chapters review neuromodulation and interventional approaches to headache management. The more invasive options presented should be considered in the context of an integrated approach to care.

The editors are most grateful to the contributing authors whose outstanding work synthesizing the available evidence and making concrete treatment recommendations have made this book possible. Our hope is that their contributions will provide clinicians with the foundation for delivering the highest quality care for headache patients and, at the same time, reduce the burden that complex, integrative medical diagnoses necessarily impose.

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Chapter 1
What Is Integrative Headache Medicine?

Lauren R. Natbony

What Is Integrative Medicine?

Integrative medicine is a patient-centered model of care that brings together mainstream and complementary treatments. As defined by the National Center for Complementary and Alternative Medicine (CAM) at the National Institutes of Health, integrative medicine "combines mainstream medical therapies and CAM therapies for which there is some high-quality scientific evidence of safety and effectiveness" [1]. It is "healing-oriented medicine that re-emphasizes the relationship between patient and physician, and integrates the best of complementary and alternative medicine with the best of conventional medicine" [2]. The integrative medicine model is guided by shared decision-making between the practitioner and the patient and an individualized therapeutic plan. The patient's background, interests, and goals are discussed and accounted for when choosing treatment modalities. From a headache and pain perspective, the goal of integrative medicine is to not only reduce and prevent pain but to improve function, quality of life, and overall wellness. The main principles of integrative medicine can be seen in Table 1.1.

What Is the Evidence for Integrative Medicine in Headache?

Understanding the evidence behind integrative treatment options and the benefits and risks can help providers discuss these modalities with their patients. Multiple studies have assessed an integrative approach to headache as a practice model.

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Table 1.1 The principles of integrative medicine

A partnership between patient and practitioner in the healing process. The partnership recognizes the uniqueness of each patient
Appropriate use of conventional and alternative methods to facilitate the body's innate healing response
Consideration of all factors that influence health, wellness, and disease, including mind, spirit, and community as well as body
A philosophy that neither rejects conventional medicine nor accepts alternative therapies uncritically
Recognition that good medicine should be based in good science, be inquiry-driven, and be open to new paradigms
Use of natural, effective, less-invasive interventions whenever possible
Use of the broader concepts of promotion of health and the prevention of illness as well as the treatment of disease
Ultimately, the patient must decide how to proceed with treatment based on values, beliefs, and available evidence
Training of practitioners to be models of health and healing, committed to the process of self-exploration and self-development

Adapted from Maizes et al. [3]

Przekop et al. evaluated a multimodal approach versus a pharmacological approach for adolescents with chronic tension-type headache. They found that the multimodal approach had a more significant effect on headache frequency and intensity [4]. Gaul et al. conducted a review of integrative, multidisciplinary headache care and concluded that this approach was effective and may help avoid headache chronification and medication overuse [5]. In a study of an integrative medicine model at the Danish Headache Center over two years, the frequency of headache decreased from 20 to 11 days per month (migraine had the most prominent reduction from 7.5 to 2.9 days per month). Absence from work significantly decreased as well [6]. Cramer and colleagues performed a prospective observational study to investigate the efficacy of an interdisciplinary, integrated care program in patients with chronic migraine and/or tension-type headache. Participants engaged in mind-body therapies, Traditional Chinese Medicine, and naturopathy and were educated about healthy lifestyle, diet, and exercise. Cognitive-behavioral therapy and mindfulness-based stress reduction aimed to improve coping skills. Headache frequency decreased from 17 to 10.6 days per month at a 6-month follow-up. There were also improvements in pain intensity, medication use, quality of life, depression, anxiety, and overall function [7].

Integrative Medicine for All Headache Patients?

All headache patients can benefit from an integrated approach, as complementary and integrative treatments can be used alongside conventional therapy. However, special consideration should be given to patients who may have challenges with

pharmacologic treatment. These patient groups include pediatric/adolescent patients, pregnant/lactating women, elderly patients, those with medication contraindications or comorbid conditions that limit medication options, patients refractory to multiple medications or who experience frequent medication intolerance, and patients with medication overuse [8]. Additionally, headache disorders accompanied by a high burden of disease may benefit from early use of integrative medicine to avoid further chronification. These headache disorders include high-frequency episodic and chronic migraine, high-frequency and chronic tension-type headache, and medication overuse headache, which are responsible for almost all headache-related burden [5].

Potential Barriers to Implementing Integrative Medicine

An integrative approach may have several barriers to implementation in clinical practice. First off, patients may not be comfortable discussing complementary therapies with their practitioners. While 28–82% of headache patients use integrative approaches, more than half do not discuss their use with their provider [9]. For those patients who may prefer non-pharmacologic therapies, insurance coverage can be an obstacle. Complementary modalities such as acupuncture, biofeedback, and neuromodulation may be unattainable in those of low socioeconomic status. Likewise, some of these modalities may be inaccessible to those who live in rural areas. From the clinician's standpoint, an integrated approach can be time-consuming and require extensive patient discussion and ongoing communication. A lack of knowledge regarding integrative modalities may also dissuade providers from discussing these options with patients. A review by Aveni et al. noted that almost 85% of providers might feel they lack the knowledge to inform their patients about complementary medicine [10]. Thus, perhaps practitioners lack guidelines regarding when and how to recommend appropriate CAM treatment.

Approach to Integrative Headache Medicine in Practice

Below is a proposed stepwise approach for incorporating integrative medicine into a headache practice. This approach allows clinicians to use standardized protocols based on conventional medicine while offering individualized, evidence-based integrative modalities. Emphasis should be placed on patients' self-efficacy and locus of control. Motivation and adherence regarding non-medical treatment options, as well as drug treatment, should be supported.

1. Conventional medical assessment and treatment: Patients are evaluated and diagnosed based on ICHD-3 criteria. Targeted pharmaceutical therapy is initiated if clinically indicated. Neutraceuticals and/or neuromodulators can be offered as the primary treatment or as supplemental therapy.

2. Lifestyle and trigger assessment: Encourage a headache diary to evaluate for potential triggers. If discovered, incorporate principles of trigger modification into the treatment plan.
3. Stress, mood, and sleep evaluation: Evaluate for depression, anxiety, insomnia, and sleep-disordered breathing. Consider referral to psychologist/psychiatrist for therapy and medication management (if needed). Consider referral to a sleep physician for sleep-disordered breathing and Cognitive Behavioral Therapy for Insomnia. Consider mindfulness training, biofeedback, progressive muscular relaxation, acupuncture, and other mind-body therapies.
4. Nutritional and metabolic evaluation and treatment: Assessment includes weight, body mass index, and nutritional assessment. Consider screening for thyroid disease and checking vitamin levels. Recommend nutritional counseling, weight loss (if indicated), and a fitness program.
5. Structural and musculoskeletal assessment and treatment: Evaluate physical fitness and potential pain contributors from the neck, cervical spine, jaw, etc. Consider referral to pain management for interventional treatment options. Recommend complementary therapies such as physical therapy, yoga, cardiovascular exercise, and acupuncture.

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Chapter 2
Identifying and Treating Underlying Medical Illness

Alison Ilana Thaler and Mark W. Green

Headache is one of the most common reasons for which people seek medical attention. Migraine, tension-type, and other primary headache disorders account for the majority of cases. Still, approximately 2–5% of patients presenting with headache will ultimately be diagnosed with secondary headache, many of which are serious and even life-threatening. This distinction between primary and secondary headache is the most important and often the most challenging step in the management of these patients. This chapter aims to review and clarify the worrisome headache "red flags" that can alert healthcare providers to a potential secondary etiology. The widely utilized mnemonic "SNOOP" was created over a decade ago to help providers remember these warning signs. As our knowledge base has increased, the mnemonic has gone through multiple iterations – most recently, "SNNOOP10" – but, for the sake of simplicity and clarity, we will use "SNOOPP" as our guide: systemic symptoms, neurologic signs and symptoms, onset, older age, pattern change, and positional quality [1]. It is important to remember that when patients have a primary headache syndrome, most commonly migraine, they are more likely to develop a headache as a symptom of these new disorders. The headache they develop is often an amplification of the preexisting one.

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Systemic Symptoms (S)

When fever is associated with headache, underlying systemic or neurologic infectious etiologies must be excluded. Common central nervous system (CNS) infections include meningitis and encephalitis. Headache is the most common presenting symptom of meningitis, reported in approximately two-thirds of cases, and is often (though not always) associated with both fever and neck stiffness. One study reported fever in approximately 46% of patients, neck stiffness in 44%, and headache in 63% [2]. Encephalitis often presents with headache and other flu-like symptoms, with headache being present in up to 80% of cases [3]. In these patients, headache is usually associated with confusion and behavioral changes. Few studies comment on the specifications of these headaches, such as the quality, location, and duration of pain, and thus such characteristics cannot be used to help guide diagnosis.

Brain abscess is another important infectious etiology to consider, though these tend to act more as mass lesions and are less often associated with fever, present in only 50% of cases. Headache is reported as the most common presenting symptom. In contrast to the headaches associated with meningitis and encephalitis, headaches occurring with brain abscesses are more likely to be associated with new focal deficits, seizures, and alteration of consciousness. The specific features of the headache (i.e., duration, location, quality) are again variable and often unhelpful in diagnosis. For example, one study found that headache duration could range from several hours to several months before presentation [4]. It's important to note that the classic triad of headache, fever, and new focal findings is uncommon, found in only 5–20% of patients [5, 6].

Overall, the combination of fever and headache is a non-specific indicator of central nervous system infections and should be most alarming when combined with other features such as neck stiffness, altered mental status, seizures, and new focal deficits.

Vasculitis must also be included in the differential diagnosis when a patient presents with headache and systemic symptoms. Giant cell arteritis (GCA), also known as temporal arteritis, is a common form of medium-to-large vessel vasculitis that causes diffuse vessel inflammation that can lead to scarring, stenosis, and eventual vessel occlusion. GCA is seen almost exclusively in patients older than 50, with a peak incidence between 70 and 80 years of age. Women are affected two to three times more often than men. As such, the diagnosis should be considered in patients over 50 who present with new headaches, especially if associated with unexplained fever or other constitutional symptoms, abrupt onset of vision changes (mainly transient monocular vision loss), or jaw or tongue claudication. Approximately 50% of patients also present with, or later develop, polymyalgia rheumatica, characterized by muscle pain and stiffness, predominantly affecting the shoulders. Most studies indicate that headache, especially, but not exclusively, located in the temples, is the most common presenting symptom (reported in 60–90% of patients), and jaw claudication is the most specific [7–9]. Headache is not invariable and can sometimes develop hours to days after the onset of other symptoms. Erythrocyte sedimentation

rate (ESR) and C-reactive protein (CRP) are generally elevated, but normal values do not exclude the diagnosis. Temporal artery biopsy remains the gold standard of diagnosis but can be negative in up to 9% of cases due to the nature of "skip" lesions and frequent steroid treatment prior to biopsy. This diagnosis can be challenging to make, and the consequences of overlooking GCA can be catastrophic, as 15–20% of patients will suffer from rapid and often irreversible vision loss if not properly treated [10]. Healthcare providers should have a low threshold to consider, screen for, and empirically treat this condition in the appropriate patient population.

The patient's immunological status is especially important to consider when headache is associated with fever or other constitutional symptoms. In patients with HIV or AIDS, headache has been reported to be among the most common pain-related complaints, second only to bilateral lower extremity pain [11]. In patients with well-controlled HIV, nearly 85% report headaches. One study found no correlation between CD4 count (500 and above) and the severity, frequency, or impact of headaches [12]. In those with poorly controlled HIV, and for patients with any degree of immunosuppression, headache is nearly always a red flag given these patients' elevated risk of opportunistic infections and predisposition to other types of dangerous CNS lesions. This risk increases with the degree of immunosuppression. The incidence of opportunistic infections, for example, dramatically increases when CD4 is less than 200 in patients with AIDS. The most common etiologies of CNS lesions in patients with advanced HIV include cerebral toxoplasmosis, progressive multifocal leukoencephalopathy, and primary CNS lymphoma, all of which frequently present with headache.

Neurologic Signs and Symptoms (N)

Headache associated with focal neurologic deficits is *always* a red flag. Ischemic stroke, intracerebral hemorrhage, and malignancy should lead the differential diagnosis, along with a variety of other vascular, neoplastic, infectious, and inflammatory etiologies. However, it is important to recognize that migraine is actually the most common etiology when headache presents with new focal deficits.

Headache is a common presenting feature of acute cerebrovascular disease. It has been reported in anywhere from 16% to 65% of transient ischemic attacks (TIAs) and non-disabling strokes, with a significantly higher percentage if the stroke is hemorrhagic. This broad range has been attributed to variations in study design, stroke subtype, and study population [13]. Stroke location does seem to correlate with the risk of associated headache. Posterior circulation strokes, for example, are significantly more likely to present with headache than anterior circulation strokes. In a large case series, headache was reported in 31% of patients with anterior circulation ischemia, independent of TIA or completed infarct, vs. 44% and 35% of patients with basilar territory infarcts and TIAs, respectively [14]. Another prospective study reported headache in 59% of patients with stroke attributed to vertebrobasilar disease vs. 26% of patients with stroke attributed to anterior

circulation disease. Cortical strokes have also been suggested to be more likely associated with headache than subcortical strokes [15].

The risk of headache at ischemic stroke or TIA onset has also been found to be significantly associated with younger age, female sex, and prior history of migraine [16]. In a retrospective analysis of patients with TIA, defined as focal brain or retinal ischemia with full resolution of symptoms within 24 hours and with negative MRI or CT, approximately 7% of patients presented with their usual headache at the time of TIA onset. More than 13% presented with a new type of headache: the majority with migraine, several with tension-type, and one with thunderclap. Of these patients, over 85% had symptoms attributable to posterior circulation ischemia. TIA patients, as compared to controls, were found to be significantly more likely to have had migraine within the previous year. This difference became even more pronounced within 1 week of TIA, particularly within the last day [17].

In patients with hemorrhagic stroke, headache is reported in nearly all patients with subarachnoid hemorrhage (SAH) as compared to approximately two-thirds of patients with intracerebral hemorrhage (ICH). This difference is likely due to the fact that the meninges are pain-sensitive, whereas the brain parenchyma is not. Headache intensity varies significantly between the two: one study reported that headache pain was rated as "incapacitating" in the majority of patients with SAH and "mild-to-moderate" in the majority of patients with ICH [15].

Overall, headache occurs more often with hemorrhagic than ischemic stroke. Within ischemic stroke, headache is more frequently associated with posterior circulation ischemia than anterior. The association of headache at stroke onset with younger age and prior headache history suggests a need to be careful when evaluating young patients with headache and focal deficits to avoid misclassification as "complex migraine." Cerebral venous sinus thrombosis (CVST) is another important vascular cause of headache associated with focal neurologic deficits and will be discussed in detail later.

Malignancy is another important etiology of headache associated with new focal deficits. Headache is a common symptom of brain tumors; however, as the sole presenting complaint of patients with brain tumors, it is rare. In the literature, approximately two-thirds of patients report headache at the time of malignancy diagnosis, but only 1–2% report headache as the sole complaint [18, 19]. As such, isolated headache rarely warrants further malignancy evaluation unless it is progressive.

Although the acuity of symptom onset is often helpful in distinguishing neoplastic from vascular causes of headache – gradual and smoldering vs. abrupt and maximal at the onset – this is not always the case. It is important to remember that neoplastic lesions can present acutely as well.

Sudden Onset (O)

Thunderclap headache is defined by the ICHD-3 (2018) as a headache that reaches maximal intensity within 60 seconds, but this limit is debatable; other than the ICHD-3, there is no consensus as to what defines "sudden" or "thunderclap" onset.

Thunderclap headache can be (and usually is) a benign condition, but it is *always* a red flag and must be emergently evaluated. Although it is often assumed to be of benign origin once subarachnoid hemorrhage (SAH) has been excluded, the differential remains broad. It includes other life-threatening vascular disorders (including reversible cerebral vasoconstriction syndrome (RCVS), cerebral venous sinus thrombosis (CVST), ischemic stroke, intracerebral hemorrhage, and arterial dissection) as well as nonvascular disorders (intracranial hypotension, meningitis, pneumocephalus).

Failure to recognize SAH can be catastrophic, as aneurysmal subarachnoid hemorrhages have a 50% mortality rate. Low volume bleeds (sentinel headaches) commonly precede the severe subarachnoid hemorrhage by a week or so, and recognizing them at that time is often lifesaving. The likelihood of SAH when presenting with thunderclap headache is variable, cited in the literature as anywhere from 10% to 30% of cases [20, 21]. Variability is likely due to referral pattern, patient population, and extent of workup that is performed. Although thunderclap headache is the classic hallmark of SAH, it is important to note that the onset of headache can be more gradual. In one study of patients referred to the emergency room for sudden onset headache and subsequently diagnosed with SAH, approximately 20% reported headache onset over 2–60 seconds, 20% over 1–5 minutes, and 20% over more than 5 minutes. Other common features associated with SAH, including nausea, neck stiffness, occipital location of headache, and impaired consciousness, should raise concern, with severity being key: only approximately 20% of patients report sudden-onset pain, and nearly 100% report "worst headache of life" [20, 22].

As mentioned earlier, CVST, dissection, and RCVS are other important vascular causes of thunderclap headache. Headache is the most common presenting symptom of CVST, reported in up to 90% of patients, and is believed to be due to a rapid increase in intracranial pressure [23]. The quality and characteristics of the headache associated with CVST are highly variable, with no specific location or pattern. Onset can be sudden but is more commonly subacute, developing over minutes to hours [24]. Internal carotid artery and vertebral artery dissection (ICAD and VAD, respectively) also often present with headache; this is more commonly reported in patients with VAD than with ICAD. Headache associated with arterial dissection is often accompanied by additional features including neck pain (reported in close to two-thirds of patients with VAD and one-third of patients with ICAD) and focal deficits related to brain and/or retinal ischemia (reported in approximately 90% of patients with VAD and 70% of patients with ICAD) [25]. RCVS is a clinical-radiographic syndrome classically characterized by recurrent thunderclap headaches and a "string of pearls" appearance on vessel imaging, thought to be due to reversible, multifocal, segmental arterial narrowing. Over 90% of these patients report one or more sudden-onset headaches prior to presentation [26]. Early associated features (occurring within the first week) include cortical SAH (20–30%), intracerebral hemorrhage (6%), seizures (3%), and posterior reversible encephalopathy syndrome (PRES) (9%). Associated ischemic events, including TIAs (16%) and CVAs (4%), occurred significantly later, most often during the second week [26, 27].

Rarely, headache can be the sole presentation of angina or myocardial infarction. Cardiac cephalalgia is defined as a headache attributed to myocardial ischemia. The clinical features are highly variable, with extreme severity and exacerbation by exertion being the most consistent. It can affect any location above the umbilicus. Several case reports, however, have reported cardiac cephalalgia presenting as thunderclap headache, suggesting that it should remain on the differential, particularly in elderly patients with no prior history of headache and significant history of atherosclerotic risk factors [28, 29].

Several primary headache disorders can also present with sudden-onset headache, but these can only be diagnosed after careful exclusion of other possible underlying etiologies. Primary cough headache is consistently provoked by sudden coughing attacks and can last seconds to hours; it is typically treated by suppressing the cough or, failing that, with indomethacin. Primary headache associated with sexual activity can also present suddenly during intercourse. It is usually bilateral, can last seconds to hours, and is treated with indomethacin or triptans 30–60 minutes before sexual activity. Primary exercise headache is reliably precipitated by sustained exercise. Duration is variable though it is typically less than 48 hours. It is indomethacin-responsive and often follows a self-limited course. Bath-related headache, triggered by bathing or other activities involving water, nearly always presents hyperacutely, consistent with thunderclap headache. Treatment is to avoid the water-related trigger; there is also some evidence that nimodipine can shorten symptom duration. Controversy exists as to whether thunderclap headache, on its own, can be a primary diagnosis in the absence of any underlying trigger or pathology. As defined by the ICHD-3 criteria, primary thunderclap headache is characterized by severe head pain with abrupt onset reaching maximal intensity in less than 60 seconds, with normal brain imaging (including vessels) and normal CSF.

Onset in Older Age (O)

New-onset headaches in patients older than age 50 should always raise concern for underlying secondary etiologies, including neoplasms, infections, and inflammatory disorders such as GCA (discussed earlier in this chapter). While secondary headaches remain much less frequent than primary headaches overall, the incidence of secondary headaches rises in this age group, accounting for approximately 15% of headaches in patients 65 and older compared to around 2–3% in patients younger than 65 [30].

A 2014 study analyzing patients with headache onset at 65 or older found that primary headaches accounted for 62% (tension-type was the most common, followed closely by migraine). Secondary headaches accounted for 16% and were most frequently attributed to cranial trauma or substance use [30]. Another, more recent study suggested that infection, cranial and cervical vascular disorders, and substance use and withdrawal are, in addition to head trauma, common and important etiologies to consider [31].

As stated above, new-onset primary headache disorders in the elderly do occur, though much less frequently than in younger individuals. The reported prevalence is anywhere from 52% to 81%, depending on the age cut-off used. Tension-type headache is the most common presentation.

Migraine attacks tend to decrease in frequency or abate altogether in patients over age 50; however, in a significant minority of patients, migraine persists. The incidence of new-onset migraine over the age of 50 is unknown, but anecdotally new-onset migraine is seen most often in a subgroup of women with migraine onset during or shortly after menopause. Clinically, these headaches often present atypically, making diagnosis challenging. Severity is often decreased, and associated features like nausea, vomiting, and photo/phonophobia are less common. Aura symptoms tend to persist into old age. It is important to note that accumulating comorbidities, particularly depression and cerebrovascular disease, often require different treatment approaches in this population. Non-pharmacologic treatment should be considered whenever possible [32]. A subset of primary headache disorders, including hypnic headache, primary thunderclap headache, and exploding head syndrome, is nearly exclusive to the elderly and should be considered in the differential.

Aside from new-onset headache, any pattern change in headache, regardless of age, though especially in the elderly, should raise red flags. Progressively worsening headache with or without new associated features can indicate underlying infectious, inflammatory, vascular, or neoplastic etiology and should be promptly evaluated.

Positional Quality (P)

Headaches that are positional, meaning that the headache worsens either upon lying down or standing up, should raise concern for underlying intracranial pressure abnormalities.

Headaches due to decreased CSF pressure are typically "orthostatic," as they occur immediately on sitting or standing up and resolve upon lying down. There are many causes for so-called "low-pressure" headaches, all of which are thought to be due to spontaneous CSF leakage from the spine. Precipitating events, such as lumbar puncture, spine surgery, or motor vehicle accidents, are often implicated, as well as conditions predisposing to dural weakness and tears, particularly connective tissue diseases such as Ehlers-Danlos, Marfan's, and autosomal dominant polycystic kidney disease [33]. As mentioned, the resultant headache is often strikingly orthostatic, though it is important to note that this feature can resolve over time. Other commonly associated features include worsening with Valsalva or exertion (which can worsen CSF leakage through meningeal tears), frequent nocturnal awakenings, tinnitus (typically non-pulsatile), and vertigo.

Postural orthostatic tachycardia syndrome (POTS) can also present with orthostatic and non-orthostatic headaches [34]. This syndrome is associated with an

inappropriately elevated heart rate when erect and improvement when supine. The diagnostic criteria include an increase in heart rate of 30 or more beats per minute (or more than 40 beats per minute in patients younger than 20) when going from supine to standing, chronic symptoms of orthostatic intolerance for at least 6 months, and other associated symptoms that are also worse when upright and improve when recumbent. Commonly, sufferers report fatigue, panic attacks, weakness, and mental cloudiness, aside from their cardiac symptoms. This syndrome is seen most often in women of childbearing years.

Headache is the most common presenting feature of idiopathic intracranial hypertension (IIH); however, these patients' headache characteristics are significantly more variable than in those with spontaneous intracranial hypotension [35]. In most cases, the headache is indistinguishable from other primary headache disorders such as tension-type and migraine, often without a positional component [36]. In a prospective study of 165 patients who met criteria for IIH, 84% presented with headache. Other associated features included transient visual obscurations (68%), back pain (53%), pulsatile tinnitus (52%), and vision loss (32%). The mean age was 29 years old, the average body mass index was 39.9, and only 2.4% were men [35]. This data suggests that IIH is almost exclusively a disease of obese young women and is likely best differentiated based on other associated clinical features and not specific headache characteristics.

Other underlying etiologies of elevated intracranial pressure must be considered when papilledema is present, including intracranial mass lesions, venous outflow obstruction, and decreased CSF absorption due to scarring following CNS infections or subarachnoid hemorrhage. Irrespective of the cause, headaches due to increased intracranial pressure tend to worsen with Valsalva.

Chiari malformations are another cause of headaches that worsen with cough or Valsalva. Chiari malformations are common, seen in close to 1% of the population, and are generally asymptomatic. However, when they cause symptoms, headache when coughing is the most common. It has been estimated that 15–20% of patients with secondary cough headache have underlying type 1 Chiari malformations. Other secondary causes of cough headache include posterior fossa lesions, subdural hematomas, and sinusitis [37]. As such, although generally benign, cough headache always warrants a careful evaluation.

Pattern Change (P)

It is traditionally taught that when a headache is due to an intracranial neoplasm, it is invariably an early morning headache that awakens one from sleep and improves as the day goes on. In reality, this "classic" brain tumor history is seen in only a minority of patients with a brain tumor. In a study of over 100 patients with primary or metastatic intracranial tumors, the majority of patients reported tension-type headaches that were as likely to worsen at night and mid-day as in the morning and often had no clear temporal variation at all [38]. So what do we look for in history

or on examination to prompt further evaluation? In this same study, the most common headache features associated with underlying mass lesions included persistent nausea and vomiting and worsening with Valsalva. In a third of those with brain tumors, the headache was the same as their preexisting headaches, but more frequent and more severe. Thus, pattern change is an incredibly important red flag. Although there is no specific quality to the headache caused by a brain tumor, the headache laterality is often a helpful localizing sign [38]. Although the brain parenchyma is relatively insensitive to pain, the meninges, extracranial arteries, and some pain-sensitive cranial nerves may contribute to headache in these patients.

Abnormal findings on neurologic examination, new-onset seizures, and worsening of prior headache syndrome are other important red flags for underlying mass lesions [39, 40]. Patients with a previously diagnosed headache syndrome are much more likely to develop headache as a symptom of a tumor than those without a history of headache, and the headache that develops is most likely to be an amplification of the patient's primary headache as opposed to a new type of headache altogether [38]. Because it is common for those with primary headaches, like migraines, to develop a brief period of worsening with a trigger that is often unclear, preexisting headache syndromes often delay tumor diagnosis. It is helpful to think of the brain tumor as simply a migraine trigger and to consider reimaging those patients that report a gradual but progressive worsening of headaches over weeks to months.

This principle is, perhaps, the most important in this chapter to remember: primary headache disorders lower the threshold for developing headaches in general. As such, almost any illness, whether neurologic or systemic, including tumors, infections, anemia, thyroid disease, and so forth, can present as worsening of a preexisting headache syndrome in patients already diagnosed with a primary headache disorder. Pattern change, therefore, should always be taken seriously and should prompt close monitoring and further evaluation.

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Chapter 3
Trigger Identification and Elimination

Robert G. Kaniecki

Introduction

Migraine is a chronic, neurobiological disorder punctuated by episodic attacks [1]. Diagnosis is determined by clinical criteria, and subcategorization is based on both qualitative (the presence or absence of aura) and quantitative (monthly headache frequency) elements. Attacks characteristically involve moderate to severe headache with an assortment of potential associated features including nausea, vomiting, and sensitivities to light and sound [2]. Nearly one-third of patients report transient visual or neurological phenomena preceding or accompanying attacks referred to as aura. The headache phase should extend between 4 and 72 hours in adults and the aura phase 5–60 minutes. Although absent from the formal diagnostic criteria, many report symptoms such as neck pain and sinus congestion or drainage. An overwhelming majority of those with episodic migraine (headaches <15 days per month), and many with chronic migraine (headache >/=15 days per month), will report symptom freedom between attacks. Despite a temporary state of wellness, an enduring predisposition to attacks warrants efforts directed towards the prevention of future attacks of migraine.

Migraine has been conceptualized as a manifestation of a central nervous system that is biologically hypersensitive and prone to episodes of disabling headache [3]. The episodes may develop spontaneously or because of a complex interplay of internal mechanisms and environmental exposures [4]. Once initiated, the migraine attack may possess not only the phases of aura and headache but also prodrome and postdrome [5]. Prodromal or premonitory symptoms may precede these other phases by hours or sometimes days, and given that timing, they may be occasionally confused as reflecting a potential triggering influence. Migraine triggers have been

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defined as “factors that, alone or in combination, induce headache attacks in susceptible individuals” [6]. Most of these influences do not result in headache in those without migraine vulnerability. Triggers are also quite specific to an individual patient, with some factors provoking headaches in some migraineurs but not in others [7]. Although some prefer to distinguish “trigger” (sufficient in isolation to reliably provoke attacks) from “risk factor” (only provokes attacks inconsistently or in combination with other risk factors), for the purposes of this discussion, the term trigger will be used.

Identification of triggers may potentially result in improved migraine control through trigger avoidance or elimination [8]. With reliable information on their triggers, patients may then be able to reduce the frequency of their attacks. They also may be empowered to employ precautionary measures at times of migraine risk. When trigger elimination, avoidance, or reduction is not possible, trigger identification may still have predictive value and inform acute treatment decisions. Deployment of certain non-pharmacologic or pharmacologic measures preemptively or in the earliest stages of acute attacks may result in improved outcomes.

The purpose of this chapter is to review the latest information available on migraine triggers. Shortcomings in methodology in the study of triggers will be reviewed. The potential impact on migraine physiology will be addressed, as will the difficulties in discerning triggers versus prodromal symptoms. Research into triggers of migraine will then be discussed, and detailed analyses of the more commonly reported triggers will be provided. The chapter will conclude with a section devoted to clinical implications of migraine trigger identification and modification as these impact patient education and management.

Methodological Issues in Migraine Trigger Research

Few randomized trials of commonly reported migraine triggers have been performed [9]. Most involved administration of a substance such as chocolate, aspartame, or red wine to a small population of those with migraine and recorded the likelihood of subsequent attacks [10]. The results of these trials may be difficult to interpret for several reasons. Sample sizes are typically small, and some have issues with blinding. Not all subjects may have expressed any prior sensitivity to the substance in question. There is also a recognized interindividual variability in migraine vulnerability that may be multifactorial and variable from week to week or even day to day.

Instead, most research studies into migraine triggers have relied on patient self-reports. Most have involved population-based or clinic-based samples asked to retrospectively recall usual triggers or identify them from a provided checklist [11]. Such work is helpful in measuring beliefs about migraine triggers or premonitory symptoms but fails to provide evidence for causation. More direct assessment of trigger-attack relationships can be conducted with paper diaries, but since many patients complete the diaries retrospectively, the data is subject to recall bias.

Prospective diary data has become the most popular means of adequately assessing potential migraine triggers [12]. Most have involved paper records that are typically completed during or following migraine attacks, introducing potential recall bias. Electronic diaries may be completed prospectively and may be time-stamped, limiting the issue of recall bias, but these are more complex to develop and more cumbersome to complete. They also may not necessarily differentiate trigger from premonitory symptom as both may precede migraine headache development. Improvements in technology, particularly with smartphones, have resulted in widened capabilities of real-time data recording and automated linking with environmental phenomena such as temperature, air pollution, barometric pressure, and levels of sleep and physical activity. Automatic downloads of information reduce patient burden and eliminate potential recall bias [13]. Analyses of digitally recorded data may also be more sophisticated and might permit the identification of those migraine risk factors producing attacks only when seen in combination. Information of higher quality can be expected from forthcoming research studies with prospective electronic diary designs.

Physiology of Migraine Triggers

Migraine is known to progress through multiple phases, but the interactions between potential migraine triggers and each of these phases remain a matter of speculation. Most research and the majority of scientific findings into the physiology of migraine have centered on the headache stage of an acute migraine attack. Just over 40 years ago, the trigeminovascular hypothesis for migraine pain was introduced [14]. Trigeminal innervation of the dura and intracranial veins and sinuses was identified as the most likely site for the origination of migraine pain. Later identification of neuropeptide mediators involved in the trigeminovascular circuitry led to crucial insights into the physiology of migraine pain and the development of an assortment of novel therapeutic agents aimed specifically at the acute treatment (triptans) and later preventive treatment (CGRP monoclonal antibodies) of migraine [15]. Despite this information, the precise relationship between migraine trigger and migraine pain has yet to be established.

Less has been known about the stages preceding the headache phase of migraine, prodrome, and aura. Since these may represent the earliest recognized steps of acute migraine in many patients, the influence of triggers on these components of migraine may be particularly interesting and relevant. Advancements in migraine neuroimaging and neurophysiology have provided recent insights into the physiological underpinnings of these phases [16]. The migraine premonitory phase or prodrome appears to primarily involve the dysfunction of integrated hypothalamic and brainstem circuits [17]. Interconnected hypothalamic nuclei have been understood to modulate and integrate external (stress, light, sleep disruption) and internal (hormone and glucose levels, hydration) factors relative to the initiation of migraine. Some have suggested this makes the hypothalamus a key candidate for integrating external

environmental migraine triggers and internal bodily signals [18]. Many of those trigger factors commonly reported by migraine patients may potentially influence hypothalamic activity. Afferent connections arrive into the hypothalamus from the cerebral cortex and olfactory and visual pathways, potentially explaining visual, auditory, and olfactory triggers. Hunger and thirst, sleep pattern changes, and hormone changes all may directly influence hypothalamic-mediated homeostatic mechanisms. Stress may impact the hypothalamus directly, or indirectly through limbic system connections. The hypothalamus may also be understood to play an important role in a threshold model of migraine pathophysiology, where triggers are proposed to reduce the threshold for subsequent acute migraine episodes [19].

Since prodrome may be absent or, due to the vague nature of the symptoms, unrecognized, aura may be the first identifiable symptom of migraine for many patients. There is substantial evidence from animal models and functional neuroimaging in humans to link symptoms of migraine aura to the electrophysiological phenomenon of cortical spreading depression (CSD) [20]. Animal models document activation of trigeminal nociceptive circuitry following activation of regions of the cerebral cortex by CSD [21]. Available data also supports the concept that CSD can lead directly to the activation of central trigeminovascular neurons involved in the headache phase of migraine [22]. Connections between migraine triggers and aura generation, however, have been difficult to establish definitively. The trigger most readily explainable would involve the effects of exposure of the occipital cortex to flashing light, a well-recognized activating factor in both migraine and epilepsy [23, 24].

Sensory triggers such as bright or flashing lights, loud or shrill sounds, and strong odors may be perceived as triggering migraine through activation of primarily cortical pathways even outside the context of CSD. Cortical connections to brainstem nuclei known to participate in pain transmission may provide the necessary network to draw a link between cerebral cortex stimulation and migraine pain development. Excitation of cortical neurons resulting from sensory stimulation or CSD, in a predisposed individual, might theoretically lead to modulation of descending inhibitory circuits impacting the function of the periaqueductal gray matter and the nucleus raphe magnus. A subsequent decline in sensory inhibition of brainstem trigeminal nociceptive pathways would then theoretically progress to the facilitation of migraine headache.

One of the challenges facing research into migraine triggers is the fact that the connection between trigger and attack is typically not absolute [25]. Patients will often describe differences in their sensitivities to those risk factors they have previously associated with the development of migraine attacks. Such variations may be identified over timelines that may be noticeable weekly to annually. An obvious clinical example is a woman describing increased sensitivity to alcohol or olfactory triggers during the menstrual cycle but not at other times of the month. Another example is the migraine patient reporting more storm-related attacks in Spring and Fall during season changes. At the same time, storms of a seemingly similar nature do not produce migraines in Summer. Such trigger discrepancies may be partly explained by variations in the prominence of the exogenous or endogenous

triggering factors themselves as increased strength or exposure to the trigger may more likely result in headache. On the other hand, there is clear evidence indicating spontaneous oscillations of hypothalamic, brainstem, and dopaminergic circuitry, which may lead to random alterations in central nervous system sensitivity and hyperexcitability [26]. A migraine attack would be proposed to ensue when the combined level of internal or external offensive forces (triggers or risk factors) supersedes the threshold set by oscillatory internal defensive forces (anti-nociceptive modulatory networks) at any given point in time. Migraine would occur when the overall level of excitation exceeds the overall level of inhibition.

Prodrome

A major challenge in the identification of headache triggers is the distinction from prodromal or premonitory symptoms warning of an impending migraine [9]. This differentiation may be difficult for several reasons. Firstly, there is a significant overlap between the symptoms reported as prodrome and influences reported as a trigger for migraine. Secondly, both would be expected to precede any aura and pain phases of migraine. Thirdly, neither is necessary nor sufficient for activating subsequent migraine with absolute reliability [27].

Recognized since the 1800s, prodrome may be reported in questionnaire-based surveys by over 80% of adults and 70% of children and adolescents with migraine [28, 29]. The most common premonitory symptoms in migraine prodrome are listed in Table 3.1. Many of these symptoms can be difficult to distinguish from migraine triggers: prodromal photophobia versus light trigger, chocolate craving versus trigger, sense of anxiety versus stress trigger, and fatigue or neck pain behaving as a prodrome or acting as a trigger. It is quite possible that certain experiences early in migraine could represent prodrome and be misinterpreted as a trigger. In one large cohort study, individuals describing migraine triggers of flashing light, certain foods, and strong odors were more likely to report the corresponding symptoms of photophobia, food cravings, and osmophobia in the prodromal stage [30].

The absolute prevalence of prodrome in migraine is difficult to definitively establish since most studies were of retrospective design and potentially altered by recall

Table 3.1 Premonitory symptoms of migraine

Constitutional	Cognitive/emotional	Sensory	Miscellaneous
Fatigue	Difficulty reading	Photophobia	Nausea
Yawning	Speech difficulties	Phonophobia	Neck pain
Hunger/cravings	Memory complaints	Scalp sensitivity	Dizziness
Thirst	Confusion/brain fog	Motion sensitivity	Urinary frequency
Myalgias	Irritability	Abnormal taste	Lacrimation
	Depression	Osmophobia	Nasal congestion
	Anxiety/stress		

bias [31]. Only two prospective studies of migraine prodrome have been conducted. The first used a prospective electronic diary study of patients preselected based on prior prodrome reported in two of three attacks [32]. The authors determined that fatigue, difficulty concentrating, neck stiffness, and photophobia were most commonly reported before ensuing migraine pain development. Those symptoms, which were most likely to predict a subsequent migraine headache attack, were difficulties with speech or reading, yawning, and emotional changes. The second study evaluated 100 patients and found premonitory symptoms preceding migraine headache in 84% [33]. Additional research into both prodrome and migraine triggers involving prospective designs is needed to contribute to the understanding of the earliest phase of migraine. Many insights into migraine pathophysiology and the relevance of migraine activating factors or triggers will likely be uncovered as more is learned from the premonitory phase of migraine [34].

Analyses of Migraine Triggers

Migraine may be provoked in susceptible individuals in scientific research settings. Exposure of most migraineurs to exogenous nitroglycerin, prostaglandin E2, and calcitonin gene-related peptide (CGRP) has been shown to incite attacks in migraine patients [35–37]. Connections between trigger and attack are nearly certain in these artificial experimental models, but linking "spontaneous" migraine with internal or external trigger factors remains significantly more challenging.

Data on migraine triggers may be obtained through a variety of approaches [9]. In clinical practice, most rely on patient self-report and diary-based information. Retrospective surveys have historically been the most common means of assessing migraine triggers, and findings can vary widely based on population assessed or study design employed. These have been administered in both population- and clinic-based settings, using unstructured recall or checklist identification of possible triggers. The prevalence of reported triggers is typically higher in clinic-based compared to community-based studies, and the use of symptom checklists also frequently increases the prevalence of triggers and the number of triggers reported [38]. Limited information is available from prospective electronic diary data, and adequately designed prospective clinical trials may be challenging to design and complete.

There is insufficient evidence to indicate any significant difference in the factors reported to trigger migraine with aura compared to migraine without aura. Several studies have indicated that changes in stress and sleep patterns are particularly relevant to those diagnosed as migraine with aura [39, 40]. Other work, however, has determined triggers are more common in migraine without aura [41]. One population-based questionnaire study of patients reporting migraine with aura found a more significant number of triggers associated with attacks without aura compared to those with aura [42]. It is not possible to draw any definitive conclusions from this limited and contradictory data.

Over the past 10–20 years, multiple studies evaluating the prevalence of various potential migraine triggers have been published [8]. Although figures vary widely, the clinical pictures reported have consistently listed a core group of risk factors reportedly producing migraine attacks. The most common symptoms are outlined in Table 3.2. Most of these trigger factors may be considered as exposing the brain to either some form of physiologic "change" or "stimulation." In symptom surveys, patients frequently mention changes in female hormone levels, weather, or sleep patterns. Overstimulation of the central nervous system with bright or flashing lights, loud or piercing noise, or certain odors are common triggers as well. Certain foods containing caffeine, nitrates, or biogenic amines such as tyramine are dietary stimulants occasionally reported as triggers. Stress, hunger, and thirst may be considered nervous system stimulants or may instead reflect a "change" triggering influence as alterations in stress levels, meal patterns, and hydration schedules may be the factors responsible for generating migraine attacks.

Kelman published the largest retrospective survey of migraine triggers when he reviewed data from 1750 patients in a clinic-based population with migraine meeting ICHD-2 criteria [43]. In this group, 75.9% reported at least one migraine trigger from unstructured recall, while 94.6% selected triggers from a provided checklist. Triggers were rated as occurring very frequently in 9%, frequently in 27%, and occasionally in 40%. The most common triggers described as occurring at least "occasionally" were stress (80%), hormone changes (65% of women), missed meals (57%), changes in weather (53%) or sleep (50%) patterns, odors (44%), alcohol (38%), excessive heat (30%), and certain foods (27%). Stress and female hormone changes were also the symptoms most commonly reported as occurring "very frequently." Through subclassification of migraine diagnoses, Kelman was able to show differences in headache profiles linked with triggers. Those reporting triggers were more likely to be diagnosed as migraine with aura or chronic migraine. Compared to those not reporting triggers, they were also more likely to report a family history of migraine, a longer history of migraine, and attacks with greater intensity, duration, and likelihood of recurrence.

A paper from Hauge described results from a population-based sample of 629 subjects meeting criteria for migraine with aura [42]. Over 80% reported triggers when provided with a checklist, and women were found to be more likely to report triggers when compared to men. The most common trigger factors in this group

Table 3.2 Commonly reported migraine triggers

"Change" triggers	"Stimulation" triggers
Increased or decreased stress ("let down")	Bright or flashing light
Female hormones	Loud or piercing sound
Missed meals	Strong odor
Altered sleep patterns	Excessive heat
Dehydration	Alcohol
Weather	Certain foods

included stress "let down" (70%), bright light (61%), intense emotional events (59%), acute stress (58%), and an altered sleep pattern (57%). From this initial study population, 181 patients completed a tailored questionnaire derived from the prior checklist [44]. When surveyed, these subjects reported the following factors were likely to trigger at least 50% of their attacks: menses (62%), bright light (47%), and emotional (42%) or physical (32%) stressors.

Several subsequent studies using clinical samples of patients with migraine showed somewhat similar results. Andress-Rothrock et al. (n = 200), Fraga et al. (n = 131), Camboim et al. (n = 123), and Wang et al. (n = 394) employed checklists to document data on migraine triggers [45–48]. Approximately 80–90% of subjects in each of these reports checked at least one trigger for migraine. Stress, menses, altered sleep patterns, bright light, odors, skipped meals, and heat exposure were most frequent. These same factors were also common in reports of Baldacci et al. (n = 120) and Menon et al. (n = 340) from clinical sample populations using unstructured recall [49, 50]. In these groups, 72.5% and 99% reported at least one migraine trigger. In the former, 100% then selected at least one trigger from a checklist, and in the latter, no gender differences in trigger reporting were identified.

Park et al. published results from a clinic-based population of patients with episodic migraine (n = 62) provided with a smartphone platform for diary completion [51]. Of 1099 total headache days evaluated, 336 were determined to be migraine and 763 non-migraine. Approximately two-thirds of migraine attacks were linked to some trigger, with the most common being stress, fatigue, sleep deprivation, or changes in female hormones or weather. Those headaches with associated triggers were determined to be more intense, more disabling, more likely to require acute medication, and more likely to meet full migraine criteria. Travel, hormone change, noise, alcohol, overeating, and stress were significantly associated with migraine as compared to non-migraine days with odds ratios ranging from 6.4 to 1.8 for travel and stress, respectively.

Many patients are keen to implicate dietary factors in the provocation of migraine attacks [52]. Most are interested in avoiding potential food and beverage culprits, and some are willing to make significant dietary adjustments. Intake of specific products or compounds may be relatively easy to restrict on a trial basis. Alcohol, specifically red wine, is one of the most commonly cited migraine triggers from a list of food and beverages [53]. Artificial sweeteners, particularly aspartame, may also be easily avoided if a relationship with migraine is suspected [54]. Dietary restriction of monosodium glutamate may be beneficial but also a bit more challenging since it is used in numerous assorted processed food products as a flavor enhancer [55]. Some studies have reviewed the merits of elimination diets in patients with purported food triggers [56]. In contrast to a high prevalence of patients reporting concerns for dietary triggers, reports from these population-based and clinical samples indicate a low proportion of patients identifying such factors [8]. The relevance of dietary triggers and corresponding patient care recommendations will be addressed elsewhere in the text.

Specific Migraine Triggers

Stress

Stress and stress "let down" are among the triggers most frequently reported in retrospective reports from patients with migraine [8, 9, 43–51]. Up to 80% of respondents in trigger surveys report a stress-related component. Most emphasize the correlation between increased stress and headache occurrence. Patients often report more frequent migraines during periods of emotional and physical stress [57]. Diary-based studies have indicated a greater likelihood of stress as measured by reported "daily hassles" within 72 hours preceding a migraine attack [58, 59]. Unfortunately, the stress-migraine relationship may be challenging to prove for several reasons. First, stress is commonly reported on both headache and non-headache days. Second, the perception of stress might actually reflect migraine prodromal symptoms of irritability, anxiety, or fatigue, which may well be present outside the context of any apparent external stressor [32]. Third, stress may result in other behavioral alterations in caffeine intake, sleep, diet, or exercise, which could increase the risk of a subsequent migraine attack.

On the other hand, many patients describe increased headache frequency during periods of stress reduction. Several studies have demonstrated a group of patients with migraine experiencing a disproportionate number of migraine attacks segregated to weekend days [60, 61]. Let down from stress is frequently cited as a major potential explanation, while other factors, such as caffeine withdrawal or oversleeping, may also be relevant [62]. Lipton et al. sought to examine the "let down" hypothesis with a study of 22 patients from a tertiary headache clinic population [63]. Of the 22 subjects, 17 completed at least 30 days of electronic diaries. Stress was assessed through two measures: the Perceived Stress Scale and the Self-Reported Stress Scale. There was no correlation between the absolute level of stress and headache occurrence. Instead, there was an association between a decline in stress over 24 hours with increased rates of migraine over the subsequent 6, 12, and 18-hour periods. Odds ratios ranged from 1.5 to 1.9 with p values <0.05 for each of these periods. Balkaya et al. published work involving familial hemiplegic migraine mice providing further scientific support for the impact of stress letdown in migraine [64]. They showed augmentation of CSD susceptibility, a surrogate marker of migraine vulnerability, in the period of relief following chronic stress. Neither acute stress nor chronic stress alone affected the susceptibility of CSD.

Houle et al. reported results linking perceived stress and migraine from a prospective cohort study conducted in primary care and clinical neurology practices in Winston-Salem, North Carolina, between 2009 and 2014 [65]. Of 100 subjects with episodic migraine, 95 completed electronic diary data on at least one migraine attack. Individuals were followed for a mean of 49 days. Entries occurred twice daily and recorded items relating to headache, mood, perceived stress, and alcohol and caffeine intake. Stress was measured by the Daily Stress Inventory. Participants

experienced headache on 1613 of 4195 (38.5%) days. The objective of the study was to develop and internally validate a headache-forecasting model for migraines associated with perceived stress. The authors were able to demonstrate the predictive utility of measurements of stress from the Daily Stress Inventory in the future occurrence of migraine attacks among this group of subjects over an extended period.

Turner et al. performed a secondary analysis of this data and proposed a scheme of characterizing headache triggers not only by possible mechanism of action but also by the "degree of surprise" to which the migraine subject is exposed [66]. The "surprise" arises from events or circumstances, which may be either rare or unexpected. In this model, headache attacks would theoretically be more likely to occur when patients are exposed to uncommon or unexpected physical or psychological challenges. Data on the number of caffeinated beverages, the number of alcoholic beverages, stress scores from the Daily Stress Inventory, and mood scores from the Profile of Mood States was collected. The probability of observing variations in each trigger was then used to estimate the "surprisal" factor for all four potential triggers. Each trigger surprisal was associated with the development of a subsequent migraine attack. The odds ratios ranged from 1.11 for alcohol to 1.30 for stress. The sum of all total trigger surprisals was associated with new-onset migraine headache with even greater reliability with an odds ratio of 1.35. Such data support the concept of migraine triggers reflecting exposure of the nervous system to internal or external environmental "change," as previously described. It also validates the position that summation of triggers may be responsible for migraine provocation in at least a subset of migraineurs.

Female Hormones

Migraine affects women disproportionally with a female to male ratio of 3:1 [67]. This female preponderance is noted once puberty is reached and continues through adulthood. It is felt that fluctuations in female hormone levels are responsible for gender differences in migraine prevalence. Menses, and sometimes ovulation, are frequently linked to migraine episodes on a monthly basis. Between menarche and menopause, approximately half of women report an association between migraine occurrences and menses [68]. Many of these women, particularly those without aura, will note an improvement in their migraines during the latter stages of pregnancy when hormone levels stabilize [69]. Following menopause, when, again, hormone levels fade and cease to fluctuate, migraine in women frequently improves and often resolves [70].

Diary and population studies have been used to confirm a link between menstruation and acute migraine. Migraine attacks have been found to occur with higher frequency before and during menses [71]. Some studies have shown these perimenstrual migraines to be more severe, less responsive to acute medication, and longer in duration with greater odds of recurrence [72]. Such information has led to the addition of two categories of menstrual migraine to the appendix of the International

Classification of Headache Disorders 3rd edition [2]. Both are diagnosed when migraine reliably occurs between 2 days prior and 3 days after the onset of menses. "Pure menstrual migraine" is applied to those women who report only these attacks, while "menstrually related migraine" is diagnosed when additional attacks may also occur outside the context of menses. Figures for prevalence among women with migraine vary widely, with estimates of 7–35% for pure menstrual migraine and 13–60% for menstrually related migraine. Although much less common and difficult to explain on a purely hormonal basis, some women describe headache occurrences with the end of menstruation [73].

Estrogen withdrawal has been proposed as the most likely mechanistic factor responsible for triggering acute migraine near menses [74, 75]. The rapid drop of estrogen levels in the luteal phase may trigger migraine through direct effects on serotonergic and opioid neurotransmitter circuits or via a reduction in the threshold for trigeminal activation. Sex hormone levels alter the responsiveness of multiple anatomic structures crucial in the physiology of migraine [76]. These include trigeminal nerve terminals in the dura, trigeminal ganglion, trigeminal nucleus, thalamus, and cerebral cortex [77–81]. Some of this altered neural responsivity may occur through modulation of secondary mediators such as CGRP. Indirect effects on migraine activation may also occur with the associated systemic escalation of proinflammatory mediators such as prostaglandins noted during the luteal phase.

The impact of hormonal manipulation adds further credence to the position that menses, and associated estrogen withdrawal, is a trigger for acute migraine [82]. One measure shown to be effective in the management of migraine at menstruation includes perimenstrual delivery of oral or percutaneous estrogen for 1 week [83]. Other strategies employed in the past have included estrogen implants and the administration of gonadotropin-releasing hormone agonists (ovarian suppression) with estrogen supplementation. Clinicians frequently now attempt to maintain more stable hormone levels in menstrual migraine patients through the use of continuous (skipped placebo tablets) low-dose monophasic combined oral contraceptives or continuous vaginal ring contraception for 12 weeks or longer [84]. Standard noncontinuous use of combined oral contraceptives in women with migraine may result in only subtle differences in the course of perimenstrual migraine or other migraine during the female reproductive years [85]. One recent meta-analysis of four studies in women with migraine demonstrated a modest reduction in numbers of migraine attacks and migraine days with the use of the progestin-only pill [86].

Environmental Conditions

Environmental conditions are frequently blamed for migraine attacks [8, 9]. Barometric pressure changes may act as a trigger for migraine associated with altitude and weather fronts. Both rainy days and sunny days have been blamed for migraine occurrences, with the former being much more common. Air quality may also potentially trigger

migraine as some have linked air pollution levels with attacks. Heat and humidity also make it to the list of purported triggers for some patients with migraine [4].

Exposure to changes in barometric pressure may occur in several non-weather settings. The ICHD recognizes specific headache disorders experienced by underwater divers and airline passengers, which may be experienced by non-migraineurs, while migraine patients may also report headache attacks associated with these activities. Ascent to high altitude, especially when rapid, may also trigger acute attacks of migraine. Davis et al. showed a history of migraine to be a risk factor for any headache at altitude (odds ratio 2.49) and migraine headache at altitude (odds ratio 14.05) [87].

The influences of weather on migraine are challenging to quantify. Any number of meteorological components may be responsible as solitary triggers or as one of a combination of factors in acute migraine episodes. Since most migraineurs report no weather triggers, pooled analyses of study populations may fail to identify potential subgroups of weather-sensitive individuals. In a diary study of 77 subjects with migraine, Prince et al. found just over half to have migraine triggered by at least one weather factor [88]. One-year calendar studies of 20 subjects from Germany and 28 from Japan showed links between migraine attacks and low air temperature, high humidity, and low barometric pressure [89, 90]. Hoffman et al. subsequently published work that indicated a subgroup of migraineurs, specifically 13 of 100 subjects, showed a significant association between their migraine events and specific meteorological parameters [91]. A few studies have shown a small correlation between weather factors and emergency department (ED) visits, specifically higher temperatures, and lower barometric pressures. In contrast, others have failed to reveal any differences associated with weather factors [92, 93]. Two studies evaluating potential links between air pollution and ED visits produced contradictory results [94, 95]. Other specific meteorological factors and a combination of factors have been reportedly linked to migraine. Martin et al. studied 90 patients in Ohio and Missouri and found an association between lightning and migraine attack frequency [96]. Li et al. followed 98 patients with migraine in the Greater Boston area over 45 days with electronic questionnaires. They found higher odds of migraine headache with high humidity in the warm season and high levels of traffic-related pollution in the cold season [97].

Some studies have been unable to show any significant correlation between weather and migraine attacks. Zebenholzer et al. published the results of a prospective, 90-day, diary-based cohort study of 238 patients with migraine [98]. They captured 11 single meteorological values at 10-minute intervals from the Central Institute of Meteorology and Geodynamics in Vienna, Austria, and used synoptic weather classification to differentiate 17 different weather situations. They found greater migraine frequencies on days with high pressure, low wind speed, and greater sunshine, but none of these were significant. In another study of 4039 emergency department patients, Villeneuve et al. found no significant relationship between ED visits and any weather condition [95]. In a narrative review, Bolay et al. suggested that data was inconclusive to implicate any individual weather factor as a trigger for migraine headache attacks [99].

Sensory Stimuli

Migraine has been conceptualized as a disorder of processing of sensory stimuli, in large part due to the clinical observations that a variety of sensory influences may trigger migraine [100]. Of the five senses, vision, hearing, and smell are the ones most likely to be affected by potential triggers as reported in migraine surveys. As discussed previously, one of the challenges of implicating sensory phenomena as a migraine trigger is the potential difficulty in distinguishing trigger from prodrome or early migraine symptomatology [32]. Flashing or bright light may represent a trigger or merely photophobia. Loud, harsh, or piercing noise may be a trigger or migraine-related phonophobia. A strong odor reaction may reflect trigger or osmophobia. Nonetheless, the potential for visual, auditory, or olfactory triggers remains quite legitimate and parsimonious with pathophysiological mechanisms of acute migraine. Activation of a genetically hyperexcitable nervous system with strong sensory stimulation could be considered a reasonable explanation for triggering an acute migraine [1, 3, 100]. In addition, deficient habituation to repeated sensory stimuli is a well-recognized neurophysiological feature seen in migraine cohorts [101, 102]. While touch and taste are not among the most relevant factors in the provocation of acute migraine, sensitivity to touch via cutaneous allodynia may become part of the migraine process in certain individuals.

Among the sensory triggers, visual stimulation appears to be most frequently reported in retrospective patient surveys [8, 9]. Some patients describe migraine provoked by light that is excessively bright or flashing, while others may report difficulty tolerating certain visual patterns such as tight or herringbone patterns of alternating dark and light colors. Emergence from a dark environment, such as a movie theater, into a much brighter environment may be difficult to handle for many complaining of an inherent sensitivity to light. Oncoming automobile headlights during night driving may be especially bothersome to many with such light sensitivity. It is not uncommon to clinically encounter migraine patients shielding their eyes with dark sunglasses. Photosensitivity and photophobia should be understood as two separate entities with potentially different physiological underpinnings. Photosensitivity can be understood as a simple sensitivity to visual stimuli. At the same time, true photophobia may be best defined as ictal sensitivity to light, producing additional aggravation of the pain of migraine [23, 103]. Photosensitivity interictally is felt to represent hypersensitivity of neurons in the primary striate and extra-striate regions of the cerebral cortex [104]. Photophobia may involve both further sensitization of these vulnerable cortical regions and increased sensitization of secondary visual pathway neurons located in the thalamus. Those patients with migraine-related photophobia or visual aura may be more likely to report interictal photosensitivity and visual triggers [23]. Various means of visual provocation of migraine have been reported. Tekatas et al. published work describing 16 patients with migraine triggered by sunlight [105]. Exposure to striped patterns was shown to incite acute migraine in papers from Harle et al. and several other groups [106]. More recent research has shown differential sensitivities based on light color. In

migraine subjects, blue frequencies are more likely, and green frequencies are less likely, to create discomfort when compared to red or amber light [107, 108].

Much less is known and written about the nature of auditory and olfactory triggers of migraine. Sound triggers are least studied among the sensory triggers. Although many patients with migraine are phonophobic during attacks, few describe significant "phonosensitivity" interictally. Those susceptible patients describe noise triggers as being loud, sharp, or shrill. Most studies show normal brainstem and auditory cortex evoked potentials interictally and variable results in habituation of auditory evoked potentials both before and during attacks of migraine [102].

Olfactory triggers are better studied, and osmophobia occurring during an acute headache is considered highly specific for migraine [109]. Patients reporting interictal "osmosensitivity" and ictal osmophobia describe quite similar olfactory triggers: strong perfumes or colognes, household cleaners and paint products, petroleum fuels or fumes, scented candles and deodorizers, and cigarette smoke [110]. In a clinic-based questionnaire study of 727 patients with migraine, Kelman found an odor trigger in 45%, with the figure reaching 62% in those subjects reporting ictal osmophobia [111]. A higher percentage of women reported odor triggers (49% vs. 22%) and osmophobia (26% vs. 18%) when compared to men. In a subsequent cross-sectional study from Fornazieri et al., 113 patients with migraine were questioned regarding various olfactory experiences associated with migraine, with 90% reporting an odor trigger [110]. Of these, 95% implicated perfume, 81% cleaning products, 72% cigarette smoke, and 71% fuel exhaust. Silva-Néto et al. demonstrated headache activation in 70% (140/200) of subjects with migraine but 0/200 of subjects with tension-type headache when exposed to strong odors [112]. These odor-triggered attacks occurred after a mean time of exposure of 25 minutes. Sensitivity to odors does not appear to arise from a lack of olfactory habituation. In contrast to data on visual or auditory stimulation, habituation to odors is normal in subjects with migraine [102]. Increased activation of brainstem and limbic system neurons has been shown following migraine induced by olfactory stimulation, implicating connections between olfactory and trigeminal nociceptive pathways [113].

Disorders of Homeostasis

Hunger, thirst, and sleep pattern disturbances have all been commonly linked with migraine development. In a large epidemiologic study from Denmark published in 1992, Rasmussen et al. determined a 70% lifetime prevalence rate for secondary headache, with the most frequent form being disorders of homeostasis (22%) [114]. Among subjects reporting headaches from disorders of homeostasis, approximately one-fifth was attributable to fasting headache. In addition to fasting provoking a secondary headache, several clinical studies have supported an association between fasting and a triggered migraine attack in predisposed individuals. From Kelman's report on 1207 clinic patients, "not eating" was a headache trigger for 57% of

migraineurs [28]. Longer fast durations have also been linked with a greater likelihood of headache precipitation [115]. Fasting, combined with other migraine risk factors, may also be responsible for the subsequent development of migraine attacks. Martin et al. subjected 56 patients with either migraine or tension-type headache to 19 hours of food deprivation and a laboratory stressor and produced headache in 93% of those exposed to both hunger and stress and 56% of those exposed to hunger without the stressor [116]. Turner et al. published subsequent work from a diary-based study of 34 subjects with migraine investigating the link between migraine and caloric intake [117]. In this group, nighttime snacking was associated with a 40% reduction in the odds of experiencing a headache compared to no food, while eating a late dinner was associated with a 22% reduction. Despite patient descriptions and these published reports, other studies have failed to identify skipped meals as a trigger for migraine [118, 119]. Some have then suggested there may be alternative origins to headaches associated with skipping of meals. Although proposed physiologic explanations have included potential impacts of hypoglycemia, caffeine withdrawal, and dehydration on the central nervous system, caloric restriction alone in the presence of unaltered caffeine and fluid intake may still result in headache activation [120]. Although no causal relationship can be established, these data indicate that further research into the mechanisms of the association between eating behaviors and headache activity is warranted.

Fluid intake may be relevant in the provocation of migraine and other headaches. It also may aggravate an ongoing migraine associated with nausea and vomiting, and rehydration is a critical part of the management of acute migraine in urgent and emergent settings. Dehydration has been felt to represent a direct or indirect factor in headaches triggered by alcohol exposure and renal dialysis [121, 122]. Even outside the setting of other illnesses or potential triggers, dehydration alone may be sufficient in inducing headache episodes. Approximately 10% of random individuals may report headache associated with dehydration when surveyed, and relief may result in minutes or hours of resumed hydration [123]. Although many clinicians advocate adequate hydration to their headache patients, the data supporting this position are sparse. Spigt et al. performed two trials examining the effects of increased water intake on headache occurrences. The first pilot study demonstrated achievement of increased water intake of 1 L/day in patients recommended to advance water by 1.5 L daily [124]. The follow-up trial of 102 subjects with recurrent "moderately intense headache" documented improved quality of life measures following 3 months of increased hydration by 1.5 L/day [125]. This study had several design flaws but did report a 47% reduction in headaches in the hydration group compared to a 25% decline in controls. Confirmation of any link between hydration status and migraine frequency requires additional research [126].

Epidemiological and clinic-based studies have long confirmed an association between migraine and sleep disorders [127]. Much of this has centered on the increased prevalence of both insomnia and sleep apnea in the migraine population. Less has been written regarding the impact of sleep disruption as a trigger for acute migraine. One clinic-based study from Kelman et al. found that short sleepers (defined as average sleep period of 6 hours) exhibited significantly more frequent

and more severe headaches than individuals who slept longer, and these subjects were more likely to exhibit headaches on awakening [128]. In retrospective clinic-based questionnaire studies, lack of sleep was reported as a significant migraine trigger by Hauge et al. and excessive sleep another trigger by Andress-Rothrock and colleagues [44, 45]. One recent cross-sectional population-based survey from Kim et al. found a prevalence of insufficient sleep among 46% of those with migraine compared to 33% with non-migraine headache and 20% of non-headache participants, but this did not allow any conclusions regarding sleep issues as a migraine trigger [129]. No attempt was made to associate sleep patterns with headache occurrences. However, the authors did note an increased sleep requirement for subjects with migraine, possibly due to the need to use sleep as a headache treatment. Sleep dysfunction does not appear to be specific to migraine headache. This same group studied sleep patterns in patients with tension-type headache (TTH) and found the prevalence of insufficient sleep was significantly higher among subjects with TTH than among those without headaches (29% vs. 20%) [130]. No well-designed prospective studies on sleep deprivation in migraine patients are presently available.

Caffeine

Patients occasionally report excessive caffeine as an activating factor in headaches, while more commonly, others describe caffeine withdrawal headache concerns. Data supporting either caffeine excess or withdrawal as a trigger for migraine are inconclusive. Caffeine is the most widely self-administered stimulant worldwide, and a significant proportion of our patients describe regular caffeine exposure [131]. In the United States and Europe, there is evidence that consumption is increasing in children, adolescents, and adults [132]. Intake may take the forms of beverages (coffee, tea, soft drinks), of non-prescription tablet supplements, or as a component of combination products containing acetaminophen, aspirin, or both. Caffeine has many positive actions on the brain [131]. It can increase alertness and well-being, help concentration, improve mood, and limit depression. It may also act as an analgesic adjuvant, leading to its inclusion in combination analgesics. Over the last decade, many have concluded that coffee/caffeine consumption is not harmful if consumed at levels of 200 mg in one sitting (around 2.5 cups of coffee) or 400 mg daily (around 5 cups of coffee) [133]. Despite several positive benefits, several studies have shown that both excessive caffeine and withdrawal from caffeine may act to trigger migraine attacks. Results from an electronic diary study of 98 patients with migraine from Mostovsky et al. demonstrated a nonlinear association between caffeinated beverage intake and odds of migraine occurrence on that same day [134]. High levels of caffeine consumption have also been linked to the development of chronic migraine [135]. The withdrawal syndrome in patients habitually exposed to caffeine may result in phenotypic migraine headaches in normal controls as well as those with a migraine predisposition, but many experience only mild nonspecific headache complaints [136].

Clinical Implications

Trigger modification or avoidance, when possible, might potentially result in improvements in headache frequency, intensity, and quality-of-life measures among patients with migraine. The World Health Organization has advocated "identification of predisposing and/or trigger factors and their avoidance through appropriate lifestyle change" as a core means of managing migraine [137]. Evidence supporting benefit from trigger avoidance or modification remains inadequate, and one controlled trial of behavioral management of migraine triggers found this approach to be ineffective [138]. Many who argue for migraine trigger modification will cite the potential benefits and the sense of empowerment transferred to the patient who assumes some level of control – and responsibility – for migraine management [8]. Others contest such a position with the perspectives that triggers are so diverse and ubiquitous that complete avoidance would result in an overly restricted lifestyle. Martin instead has proposed that a better strategy might be to first provide functional recommendations, which permit the patient to cope with potential triggers instead of following a path of avoidance [139]. A compromise between total trigger avoidance and mere trigger coping might be optimal. Identification of the triggers specific to the individual patient, and direct modification of only these factors, might provide the best balance of maximal disease improvement and minimal lifestyle adjustment. The advice would be to make only the most necessary changes.

Any program containing trigger management in those with migraine must then begin with potential trigger identification [140]. Maintenance of a diary is essential, particularly early in the course of treatment. At a minimum, the diary should contain information on days with headache, specifics on headache treatment, and lists of potential triggers [141]. Patients should be educated to expect that many of the headaches may occur without a clear trigger because they may arise through random chance or as a result of an unrecognized combination of trigger factors.

Basic principles of trigger "modification" can certainly be inserted into a migraine management program with minimal disruption of the life of the patient [142]. Such a program might help even those without any identifiable migraine trigger. These recommendations might also provide additional benefit to the general health of patients outside the arena of headache control. Any improvements resulting from a "lifestyle program" also could potentially result in decreased use of pharmaceuticals and medical resources. Additionally, patients often profess a keen interest in "natural" means of migraine management, and such steps are frequently preferred over pharmacologic steps that have costs and potential side effects [143].

The variety of options available to patients should be discussed during the development of a comprehensive migraine management program. Preferences of the individual patient should be integrated into the decision process [144]. Dietary modification with minimization of additives, preservatives, and artificial sweeteners, regular exercise, moderation of alcohol intake, and avoidance of nicotine are all recommendations appropriate to any migraine patient. However, these have been addressed in other chapters. Recommendations covered in Table 3.3 are based on

Table 3.3 Migraine trigger modification and lifestyle program

Potential trigger	Lifestyle recommendations
Stress	Stress management, relaxation strategies (prayer, meditation, yoga), cognitive behavioral therapy, biofeedback
Sleep deficit or excess	Sleep regular hours, avoid naps, and practice good sleep hygiene
Hunger/skipped meals	Eat 4–6 small portions daily
Dehydration	Drink 2 L (women) to 3 L (men) of water daily

the information provided explicitly in this chapter. Since we previously referred to the physiological impact of triggers as representing exposure of a predisposed hypersensitive nervous system to either "change" or "overstimulation," the themes in the lifestyle program can be simplified with the terms "regulation" and "moderation." Certain triggers discussed in the text are not included in the table due to lack of modifiability or complexity of management. Avoidance of environmental or weather factors may be impossible. Management of hormonally related migraine is complex and may require medical management as outlined in the text. Despite these shortfalls, the identification and management of triggers specific to the patient combined with a healthy lifestyle regimen might indeed result in improved headache control and quality of life.

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Chapter 4
A Prescription for Exercise

Marianna Shnayderman Yugrakh

Introduction

Assessments of physical activity and recommendations to exercise have been a routine part of the evaluation of patients with various headache disorders. There is a great deal of exciting research in the field to support these recommendations. A recent meta-analysis supports aerobic exercise intervention for reduction of migraine frequency [1], and one trial showed that vigorous aerobic physical activity 3 days per week for 40 min at a time was as effective as preventive treatment with topiramate [2]. Several studies support the use of low-load endurance craniocervical and cervicoscapular exercise for tension-type headache [3]. Guidelines now suggest an early return to graduated aerobic exercise training for the amelioration of concussion-related symptoms, including post-traumatic headache [4]. The mechanisms by which exercise improves headache symptoms are not fully elucidated. They may include neuroinflammatory, neuromodulatory, cerebrovascular, and psychological effects in migraine, as well as muscle control of cervicoscapular region in tension-type and cervicogenic headache. In reviewing data for various exercise programs, it is important to keep in mind that every prescription for exercise should be individualized to a patient's level of fitness, should include a combination of aerobic fitness as well as strength exercises as per guidelines for all healthy adults [5], and should specify intensity, frequency, and duration of exercise that may benefit a specific headache disorder.

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Pathophysiology of Exercise and Its Effect on Headache Disorders

Exercise is physical activity that is planned and structured for improvement or maintenance of physical fitness. Some of the components of physical fitness include cardiorespiratory endurance, muscular strength and endurance, and body composition. Aerobic exercise, or endurance training, involves movement of large muscles in a rhythmic manner for sustained periods. It is performed at submaximal intensities such that the cardiovascular system can supply oxygen for the activity, and it is designed to increase cardiovascular and respiratory fitness. Strength exercises, or resistance training, can be performed using bodyweight resistance, free weights, elastic bands, or machines. Mobility and balance focused are other types of exercise [6].

A prospective cross-sectional study from Norway showed that migraine and other headache disorders were more likely in individuals with a low level of physical activity [7]. A follow-up large cross-sectional study found that adults under age 50, with lower physical fitness measured by peak oxygen uptake, had an odds ratio of 3.7 for migraine and 1.8 for tension-type headache [8]. Though these studies cannot suggest causality, physical activity is associated with reversion of chronic migraine into episodic [9]. It is identified as a protective factor, increasing the threshold for migraine attacks [10], and has been associated with a reduction in migraine frequency [1].

Physical exercise is an essential part of the treatment of many patients with chronic pain and depression. The role of exercise in headache pathophysiology is multifactorial and disorder-specific. Most of the research has focused on migraine-related effects, with a paucity of data in tension-type headache. Exercise may affect headache preventively and acutely. There are biomarkers and mechanisms that are common to aerobic exercise and migraine. These markers and related processes fall into neuroinflammatory, cerebrovascular, neuromodulatory, cortical spreading depression, hormonal, as well as psychopathologic and social-cognitive categories [11].

Neurogenic inflammation is recognized in migraine [12, 13] and is a pathway considered in the beneficial effects of exercise [11]. Elevations in systemic inflammatory marker concentrations, including C-reactive protein (CRP) and alternations in adipocytokines (TNFα, interleukin-6, interleukin-1β), have been implicated in migraine pathogenesis [14–16]. Obesity, associated with an elevation of these markers [17, 18], is a risk factor for migraine [19, 20]. It is hypothesized that chronic inflammation may enhance peripheral trigeminovascular inflammation, promoting trigeminal sensitization and migraine chronification [13, 19]. Long-term physical activity is associated with a reduction of inflammatory markers, including CRP, TNFα, and interleukin-6 [21, 22], in patients with various underlying disorders. Higher plasma concentrations of a pro-inflammatory, hyperalgesia promoting, and anxiety associated cytokine, IL-12p70, have been found in patients with migraine. Regular moderate aerobic exercise training for 12 weeks resulted in a significant reduction in plasma IL-12p70 concentrations [23].

Migraine is a neurovascular disorder with several cerebrovascular biomarkers and mechanisms linking it to exercise. These include vasomotor tone, nitric oxide,

vasovagal activity, and cerebral blood flow [11]. There is strong evidence for a dose-response relationship between physical activity and cardiovascular health. In migraine patients, regular aerobic exercise increases peak oxygen uptake (a maker of cardiorespiratory fitness related to the functional capacity of the heart and oxygen use by tissues) [2]. Further, an inverse relationship has been shown between the presence of headache and peak oxygen uptake [8]. Increased risk for cardiovascular disease is consistently described in patients with migraine [24–26]. Some of the proposed underlying mechanisms include endothelial dysfunction, hypercoagulability, vasospasm, and cardiovascular risk factors. Exercise can help reduce these risk factors. Regular physical activity is associated with reduced resting blood pressure, increased high-density lipoprotein cholesterol, reduced body fat and intra-abdominal fat, improved glucose tolerance, and reduced blood platelet adhesiveness and aggregation [6].

Neuromodulatory effects of exercise may be exerted via endogenous opioids, endocannabinoids, serotonin, calcitonin gene-related peptide (CGRP), and brain-derived neurotrophic factor [11, 27]. Beta-endorphin, an endogenous opioid, was one of the earliest peptides investigated for its role in analgesia during exercise. It is released during painful or stressful events, has a high binding affinity to the μ-opioid receptor, and suppresses pain at spinal and supraspinal targets. Patients with migraine have lower β-endorphin levels in CSF [27, 28], and plasma [29, 30], with lower levels inversely related to the frequency of migraine, and reduced levels both ictally and interictally. The effect of exercise on β-endorphin levels has been variable. At vigorous intensity or when prolonged, aerobic exercise is more clearly associated with acutely increased β-endorphin levels [27, 31]. Parallel to this, aerobic exercise increases pain thresholds acutely, and the largest effect is found when exercise is performed at high intensity and longer duration [32].

The chronic effect of exercise on β-endorphin levels and headache was investigated in patients with low-frequency migraine. Patients exercised on a treadmill by gradually increasing effort to a submaximal capacity (80% of maximal heart rate), stopping after 10 min. β-Endorphin was measured from blood samples pre- and post-exercise, and the latter was significantly higher. Patients then exercised three times per week for 6 weeks, each session lasting 40 min with 20 min at 60% of maximal heart rate. β-Endorphin levels were again evaluated at the end of the exercise program. The mean level after exercise in subjects that completed the exercise program was statistically higher than the baseline level, and attack frequency and intensity of migraine headaches were reduced [33].

Intense aerobic exercise can also increase levels of endogenous cannabinoid or endocannabinoid, anandamide [34]. A runner's high or sense of well-being consisting of reduced anxiety, analgesia, and euphoria was thought to be a β-endorphin effect, but has more recently been attributed to anandamide; several of these characteristic responses to exercise were inhibited specifically by cannabinoid receptor blockade [35]. Central and peripheral endocannabinoids are produced with exercise. In addition to analgesic effects through central descending modulation of pain, endocannabinoids have effects on sensory afferents [27, 36, 37]. Patients with chronic migraine and medication overuse headache have lower anandamide levels in plasma and CSF, and dysregulation of the endocannabinoid system is postulated in migraine [27, 38]. The effects of exercise on endocannabinoids in patients with

migraine warrant further investigation, as does the interaction between endocannabinoid and opioid systems in these patients.

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is broadly expressed in the brain where it plays a role in neuroplasticity in addition to modulation of pain signaling. Acutely, BDNF levels rise in response to aerobic exercise, but not most strength training, and regular aerobic exercise increases resting BDNF levels released from the brain [39–41]. In trigeminal ganglion neurons, BDNF is released in response to inflammatory mediators and affects synaptic plasticity in the trigeminal nociceptive pathway, an antinociceptive and protective strategy [27]. Exercise-related improvement of cognitive function has been linked to BDNF increases in several studies [39], and specifically, in migraine patients, an aerobic exercise program improved central information processing [42].

CGRP is a neuropeptide that is central to migraine pathophysiology. In addition to its roles in neurogenic inflammation and compensatory vasodilation, it has neuromodulatory effects on the trigeminovascular system as well as central pain processing pathways, including in the hypothalamus and more broadly [43]. Migraine preventive therapies, including CGRP monoclonal antibodies and onabotulinumtoxinA, reduce CGRP activity or its release/levels [44]. There are conflicting findings regarding changes in CGRP after exercise [27], and future clinical trials of aerobic exercise programs for migraine should include this biomarker.

Psychological effects of exercise include self-management, as well as effects on mood, anxiety, and stress. Exercise, as a behavioral intervention, may improve one's sense of confidence and ability (or self-efficacy) for migraine self-management [11, 45, 46]. There is a high prevalence of psychiatric comorbidity in patients with migraine and chronic tension-type headache, and depression and anxiety are associated with the chronification of migraine. Both aerobic and resistance training reduce depression symptoms [47]. Aerobic exercise is effective in improving anxiety symptoms in patients with a diagnosis of anxiety or stress-related disorders [48].

Beyond the direct effects of pain modulation, aerobic exercise training is effective in the treatment of multiple migraine comorbidities, including cardiovascular disorders, obesity, sleep disorders, and anxiety and depression. Many of these are risk factors for chronification of migraine. Additionally, in adults, the benefits of regular physical activity also include lowered risk of all-cause mortality, reduced risk of dementia and multiple cancers, as well as improved bone health and physical function [5].

Designing an Exercise Program: A Prescription for Exercise

A prescription for an exercise program should (1) be individualized to a patient's level of fitness and their goals; (2) include a combination of aerobic fitness as well as strength exercises; and (3) specify intensity, frequency, and duration of exercise.

Aerobic exercise, or endurance training, is achieved via brisk walking, jogging or running, cycling or elliptical work, rowing, or swimming. In 2018, Physical Activity Guidelines for Americans (PAG) were developed by a federal advisory committee and the Department of Health and Human Services, after reviewing current science and evidence about physical activity and health. It recommends that

adults should perform 150–300 min a week of moderate-intensity, or 75–150 min a week of vigorous-intensity, aerobic physical activity, or an equivalent combination for overall health benefits [5]. The exercise intervention clinical trials in migraine, detailed in the next section, used similar parameters. The total weekly time required for aerobic exercise can be broken down across 3 or more days. Spreading the weekly time across several days, and even in 10-min bouts of exercise, provides similar cardiovascular and pulmonary benefits as 30-min sessions [5, 49]. The PAG suggests that for overall health benefits, bouts of a prescribed duration are not essential. Spreading exercise over several sessions, instead of 1–2 very long sessions, decreases the risk of musculoskeletal injury and cardiovascular events [50].

Warm-up and cool down are essential elements of a program to reduce the risk of injury associated with exercise. The planned activity can be started at lower intensity and speed for 5–10 min for a warm-up to allow the body to prepare for more vigorous activity. A cool down for 5–10 min after strenuous exercise can aid recovery and prevent exercise-associated postural hypotension. Exercise should be gradually increased over time via intensity, frequency, and duration to reduce the risk of injury [6]. When starting an exercise program in an inactive patient, increasing the duration of light to moderate activity is recommended. An increase in time per session of 5–10 min every 1–2 weeks over the first 4–6 weeks is reasonable for the average adult [50]. After that, both intensity and duration can be gradually increased. This slow introduction to exercise reduces the risk of cardiac events in sedentary individuals.

The intensity of aerobic exercise can be quantified in absolute and relative measures. Relative intensity is the level of effort to do an activity compared with a patient's capacity or fitness. A simple gauge for intensity is the "talk test": during moderate-intensity exercise, a person is too winded to sing but can talk. During vigorous-intensity exercise, a person has difficulty maintaining a conversation. Relative intensity can be measured via the heart rate or oxygen uptake. Moderate-intensity activity can be attained via a 64–76% maximal heart rate, while vigorous activity occurs in the range of 77–100% of maximal heart rate. The maximal heart rate (HR_{max}) is the highest value obtained during peak exercise and can be estimated by different equations; the most commonly used is $HR_{max} = 220 - \text{age}$. Several regression equations may be more accurate. One that applies to a population of men and women with a broad range of age and fitness levels is $HR_{max} = 207 - (0.7 \times \text{age})$ [6]. The intensity of exercise can then be prescribed as a range of target heart rates and calculating maximum and minimum in the range using the equation: target HR = ($HR_{max} \times$ % intensity desired). The % intensity desired ranges are summarized in Table 4.1. Another method of calculation is based on heart rate reserve (HRR), which is the difference between maximum heart rate and easily measured resting

Table 4.1 Estimation of intensity of aerobic exercise

Intensity	%HRR	$\%HR_{max}$	Rating of perceived exertion (RPE)
Light	30–39	57–63	9–11
Moderate	40–59	64–76	12–13
Vigorous	60–89	77–95	14–17
Near maximal	≥90	≥96	≥18

Adapted from ACSM's Guidelines [6, 50]
HRR heart rate reserve, HR_{max} maximum heart rate

heart rate (HR_{rest}). The target heart rate range for the desired intensities can be calculated via the equation: target HR = [($HR_{max} - HR_{rest}$) × % intensity desired] + HR_{rest}. For example, for a patient who is a 48-year-old woman with a resting heart rate of 75 bpm, a prescription for moderate-intensity exercise would recommend that she stay in the target HR range 114–124. The calculation based on:

1. $HR_{max} = 207 - (0.7 \times age) = 207 - (0.7 \times 48) = 173$
2. Desired range of exercise intensity based on heart rate reserve, obtained from Table 4.1, of 40–50%
3. Target HR minimum = [($HR_{max} - HR_{rest}$) × % intensity desired] + HR_{rest} = [(173 − 75) × 0.4] + 75 = 114
4. Target HR maximum = [(173 − 75) × 0.5] + 75 = 124

Absolute intensity, or the amount of energy expended during the activity, is expressed in metabolic equivalents of a task, or MET units. Exercise intensity is estimated by comparing oxygen consumption during activity with consumption during rest.

Exertion with exercise is also assessed from a patient's perspective via the rating of perceived exertion (RPE). Most commonly, it is rated on the Borg scale of 6–20. RPE is a standard measure in clinical trials of exercise for headache.

High-intensity interval training (HIIT) involves intermittent, usually regularly timed bouts of high-intensity activity alternating with brief periods of rest or low-intensity activity. HIIT has been compared to moderate-intensity continuous exercise (MCT) and has been shown to induce more significant increases in cardiorespiratory fitness when total work performed during training is comparable [51, 52]. One randomized controlled trial comparing aerobic programs in migraine patients found HIIT to be more effective than MCT for the reduction of migraine frequency, detailed in Table 4.2 [53].

Another important element of an exercise program is strength training. Higher levels of muscular strength are associated with better cardiometabolic risk factor profile and lower risk of all-cause mortality [50]. For general muscular fitness, an individual should resistance train each major muscle group (chest, shoulders, upper and lower back, abdomen, hips, legs) 2–3 days per week. Strength exercise, or resistance training, can be achieved with free weights, resistance machines, or resistance bands. Each muscle group should be trained for two to four sets. A resistance exercise that allows one to complete 8–12 repetitions per set should be selected to increase muscle strength and mass. For endurance training, a lower resistance should be chosen to allow for 15–25 repetitions [6]. There should be a strong focus on core strengthening to improve posture and reduce neck pain, both of which may feed into migraine or cause cervicogenic headache. The benefit of core strengthening is further detailed in the evidence sections below.

Regular exercise is best achieved when activities that are selected are (1) enjoyable, (2) easily accessible, and (3) scheduled into protected time. Goal setting is a beneficial cognitive strategy for increasing physical activity behavior. Goals should be precise and quantifiable, such as achieving a particular distance or participating in a competition, and realistic, with a specific time frame [6]. Other strategies include planned rewards and social support of workout partners.

Details of exercise programs studied for the treatment of specific headache disorders are included in the section below.

Table 4.2 Controlled trials of exercise intervention for migraine

Study ref	Study design, subjects included	Exercise intervention and control	Results
Studies focused on aerobic intervention alone			
Darabaneanu et al. (2011)[a] [54]	Controlled trial 10-week intervention → 8-week follow-up 16 patients with 2–8 migraine attacks/month No aerobic exercise for 6 months prior No prophylactic meds	Exercise: 10-week intervention jogging 3×/week supervised 1/3 sessions allowed at home 50 min sessions: 10 min warm-up 30 min vigorous jogging 10 min cool down First 5 weeks interval training of jogging/walking performed building up jogging from a few min up to 30 Intensity: 60–75% maximal oxygen uptake (vigorous) Control: no intervention	Primary endpoint: number of migraine days per month significantly lower with Exercise 3.8 → 2.3 (−1.5) Than control 3.3 → 3.6 (+0.3) Intensity of headache attacks and duration of headache attacks were also significantly lower Secondary endpoint: 62% of patients in the exercise group were "treatment responders" with at least 50% reduction in migraine days Fitness levels (physical cardiopulmonary working capacity) significantly improved after training
Varkey et al. (2011)[a] [2]	Randomized, controlled 12-week intervention → 3 and 6 months post tx follow-up for 4 weeks each 91 subjects with 2–8 migraine attacks/month Age 18–65 No regular exercise for 3 prior months No prophylactic meds	Exercise: 3×/week, supervised, up to 2 at home allowed Indoor cycling 3×/week 40 min sessions: 15 min warming-up 20 min vigorous exercise 5 min cool down Intensity: RPE scale 14–16 (vigorous) Control: (1) Topiramate 25–200 mg/day, weekly increase by 25 mg to highest tolerated (2) Relaxation – scheduled individual relaxation exercises 5–20 min each, daily home practice	Primary endpoint: Change in migraine attacks during the last month of treatment vs. baseline – no significant difference between groups Exercise −0.93 (4.3 baseline attacks, 7 baseline days) Relaxation −0.83 (4.2 baseline attacks, 7.6 baseline days) Topiramate −0.97 (3.6 baseline attacks, 7.5 baseline days) Secondary endpoint: Maximal oxygen uptake increased significantly in exercise group Reduction in pain intensity significantly favored topiramate group at 3 months, though no difference in proportion of subjects with a change in pain intensity

(continued)

Table 4.2 (continued)

Study ref	Study design, subjects included	Exercise intervention and control	Results
Santiago et al. (2014)[a] [55]	Randomized, controlled 12 weeks intervention → 12-week follow-up 60 patients with Chronic migraine No exercise for 3 prior months No prophylactic meds Age 18–50	Exercise: 3×/week fast walking for 40 min, supervised weekly by phone with amitriptyline 25 mg daily Intensity: instruction for walking fast Control: amitriptyline 25 mg daily alone	Primary endpoint: Change in migraine days per month during the last month of treatment vs. baseline – significantly lower in exercise group Exercise + amitriptyline: 23 → 5 Amitriptyline: 25 → 13 Secondary endpoint: Duration of headaches, severe intensity of headaches, BMI, and Beck depression and anxiety inventory – significant improvement was seen with exercise
Hanssen et al. (2017)[a] [53]	Randomized, controlled 12-week intervention → immediate assessment 45 patients with With EM without aura No prior exercise for 6 months No prophylactic meds No h/o cardiovascular disease	Exercise: Equal warm-up and cool down for both intervention groups followed by (1) HIIT: 2×/week, running intervals of 4 min 90–95% HR_{max} followed by 3 min rest 70% HR_{max}, repeated four times (vigorous peak intensity) (2) MCT: 2×/week, running at upper-moderate intensity of 70% HR_{max}, for 45 min (moderate) Control: maintain daily physical activity, standard physical activity recommendations	Primary endpoint: Change in number of migraine days not statistically significant between groups HIIT: 3.8 → 1.4 (−2.4) MCT: 4.5 → 3.2 (−1.3) Control: 3.2 → 2.0 (−1.2) Secondary endpoint: Retinal vessel diameters and physical fitness markers including maximal oxygen uptake and lactate threshold, the latter of which was significantly better with HIIT intervention compared to others

Study ref	Study design, subjects included	Exercise intervention and control	Results
Olivera et al. (2017) [23]	Randomized, controlled 12-week intervention → immediate assessment including blood sampling 20 female patients With EM without aura No prior exercise for 12 months No prophylactic meds in the past Age 20–50	Exercise: 3×/week, supervised 40 min: 5 min warm-up 30 min walking on treadmill 5 min cool down Intensity: an average 50–55% maximal oxygen uptake (moderate) Control: waiting list	Primary endpoint: Change in number of migraine days from baseline to last 4 weeks of intervention, significantly reduced in intervention group Exercise: 8.5 → 4.8 (−3.7) Control: 7.8 → 8.2 (+0.4) Secondary endpoint: IL-12p70 levels significantly reduced in exercise group after intervention, not control group; with positive correlation to reduction in number of migraine days GAD7 scores significantly reduced in exercise group after intervention, not control group
Kroll et al. (2018)[a] [57]	Randomized, controlled 3-month intervention → 3 months after follow-up 70 patients with ≥2 migraine days per month + ≥1 TTH day per month + ≥1 day neck pain per month (no trauma or cervical path) Continue adjusting prophylactic meds	Exercise: 3×/ week – once supervised at least once a week cycling and at least once a week on elliptical cross-trainer/brisk walking/running once a week min 45 min session: 10 min warm-up 30 min vigorous exercise 5 min cool down Intensity: RPE scale 14–16 (vigorous) Control: maintain daily physical activity	Primary endpoint: Change in number of migraine days post-treatment: reduced from 9.2 to 7.2; no difference between groups Secondary endpoint: Exercise group showed better fitness after treatment, improved ability to perform activities

(continued)

Table 4.2 (continued)

Study ref	Study design, subjects included	Exercise intervention and control	Results
Studies that combine aerobic activity with other intervention not controlled for (indicated by +)			
Bond et al. (2018)[a] [58]	Randomized, controlled 16-week exercise → assess 4 weeks after intervention, again 4 months after intervention 110 female patients Age 18–50 BMI ≥ 25 ≥3 migraine attacks over prior 3 months Continue stable prophylactic meds	Exercise: Gradually progressed exercise to goal of 250 min/week 5×/week home-based + standard calorie- and fat-restricted diet, and behavioral strategies for weight loss Intensity: "moderate" Control: migraine education, self-management without focus on weight loss or exercise	Primary endpoint: Change in number of migraine days post-treatment: no difference in reduction in migraine days between the groups (−3 vs. −4 days), or at follow-up Secondary endpoint: 3.8 kg weight loss post-treatment and 3.2 kg weight loss at fu in weight loss group; this 3.3% weight loss may not be clinically meaningful (5% threshold)
Narin et al. (2003) [59]	Controlled trial, alternate non-random allocation 8-week intervention → immediate assessment, including blood sampling 40 female patients Age 20–50 ≥4 migraine attacks/month No history of sports participation	Exercise: 3×/week, supervised 1 h session: 5 min warm-up 10 min cycling 10 min walking 5 min stepper +10 min upper extremities resistance training + neck and posture exercises (10 reps) + rowing 10 reps 5 min cool down Intensity: "moderate" Control: no intervention	Primary endpoint: Frequency of headache after intervention Exercise: 7.4 → 3.6 days Control: 8.9 → 7.0 (no significant baseline difference, significant intervention intergroup difference) Secondary endpoint: NO levels from blood samples collected in morning at rest pre and post-intervention levels significantly increased in exercise group compared to control

Study ref	Study design, subjects included	Exercise intervention and control	Results
Lemstra et al. (2002) [60]	Randomized, controlled 6-week intervention → immediate and 3 months after follow-up 80 patients with Chronic migraine >Age 18	Exercise: 18 group sessions of aerobic activity, supervised + strength training +2 lectures on stress management and relaxation training +1 dietary goals lecture +2 massage therapy sessions Intensity: "submaximal aerobic exercise" Control: waiting list and standard medical care	Primary endpoint: Change in self-perceived days of pain in the prior month – significant reduction with intervention Intervention: −9.5 Control: −1.3 Statistically significant change in pain intensity, duration, both immediately and at 3 months
Dittrich et al. (2008) [61]	Randomized, controlled 6-week intervention 30 female patients Chronic migraine >Age 18	Exercise: 2×/week 45 min gymnastics with music: 5 min warm-up 15–20 min aerobic exercise 10–20 min strength training 5 min stretching +15 min progressive relaxation Control: received study information about potential effects of PT	Primary endpoint: Migraine frequency and intensity self-rating significantly reduced between groups Secondary endpoint: Quality of life, Beck depression inventory without significant difference between groups

[a]Studies included in meta-analysis [1]

BMI body mass index, *HIIT* high-intensity interval training, *MCT* moderate continuous training, *RPE* rating of perceived exertion, *TTH* tension-type headache

Evidence for Exercise in Migraine

Aerobic exercise for the prevention of migraine has been assessed in multiple randomized clinical trials (RCT). These examined aerobic exercise interventions for 6–16 weeks, the majority for 3 months, in subjects with episodic migraine and in one study with chronic migraine. Exercise interventions included walking, jogging, cycling, and elliptical exercise (using a cross-trainer). Intensity targets were moderate to vigorous. Training occurred at least three times per week in most studies, with a range of two to five times per week. The summary of controlled trials can be found in Table 4.2.

A meta-analysis of six controlled trials, most randomized (marked with superscript "a" in Table 4.2), found a statistically significant reduction in the number of migraine days after a 10–12-week aerobic exercise treatment with a mean reduction of 0.6 ± 0.3 migraine days per month compared to controls [1]. A moderate reduction in pain intensity (20–54%) was also seen. There were no adverse side effects of exercise reported in any of the trials. Some of the studies included controls of migraine education, relaxation, standard physical activity, and migraine preventive pharmacological therapy. They did not confer significant differences with aerobic activity intervention lowering the pooled effect size. The studies that did not have an active control group [54, 55] had a higher migraine day reduction.

Another meta-analysis assessed the effectiveness of interventions used by physiotherapists on intensity, frequency, and duration of migraine, tension-type headache, and cervicogenic headache [56]. In migraine patients, four studies of aerobic exercise showed a reduction in headache frequency of −1.63 days and a reduction in the duration of headache of −15.8 h. There were no studies available regarding strength training effects.

In comparison to the standard of care pharmacological prevention, exercise has been found to be non-inferior. One well-designed randomized controlled trial showed that a vigorous exercise program for 12 weeks was as effective as topiramate for reduction of migraine frequency. Patients with moderate-frequency episodic migraine were randomized to receive a 12-week intervention with (1) vigorous aerobic exercise (40 min three times a week) or (2) topiramate (dose up to 200 mg daily) or (3) weekly relaxation training and daily home relaxation. All three groups had a comparable reduction of migraine attacks and days, detailed in Table 4.1. The exercise group had significantly increased maximal oxygen uptake and no adverse effects. Further, the benefit of the treatment was sustained at 3 and 6 months [2]. In another study, the combination of aerobic exercise and amitriptyline reduced the number of migraine days significantly more than amitriptyline alone, though a low dose of the TCA was used in the trial [55].

In summary, clinical trials of aerobic exercise suggest that moderate to vigorous aerobic activity, performed 3 days per week for 40–50 min, is beneficial for the reduction of migraine frequency, possibly migraine intensity, and should be considered as a preventive treatment of migraine. The limitation of currently available studies is the

lack of data on the comparison of different aerobic exercise protocols or dose-response assessments. Longer duration of exercise intervention has also not been examined.

There are no specific studies evaluating strength training or stretching for migraine symptoms. Shoulder and neck pain are common symptoms of migraine [62], attributed in part to trigeminal-cervical complex activation as one of the central processes in migraine. A controlled study examined neck flexor and extensor endurance in women with migraine and age-matched control women without migraine and found significantly reduced endurance in subjects with migraine, with a similar level of reported neck pain during testing [63]. Thus, a cervical strengthening program under the guidance of a physical therapist should be considered as a remedy. Low-load endurance craniocervical and cervicoscapular exercises, as described in tension-type headache therapy section, may be appropriate. A home exercise program consisting of neck stretching exercise while seated in a chair, shoulder stretching, and forehead and occipital ball rolling has been proposed [64].

Exercise as a Trigger for Migraine

Paradoxically, exacerbation of headache by physical activity is a diagnostic feature of migraine. Exercise has been described as a trigger for migraine in retrospective surveys with variable rates (22–38%) [65–67]. These types of studies can be affected by recall bias. In prospective studies of patients who self-report the trigger, migraine is triggered inconsistently. One provocation study examined the effect of 1 h-long strenuous running or cycling (reaching 80% HR_{max}) on subjects who reported exercise as a trigger for their migraines. An attack was triggered in 4 of 12 subjects within 3 h of exercise [68]. In another prospective trial, patients with migraine who reported exercise as a trigger performed vigorous-intensity cycling, with ramping up of power until subjects were exhausted (>17 RPE or could not keep up with >40 revolutions per minute). Migraine starting within 24 h of this test was considered triggered. Twenty-one percent of the 14 patients that performed the test twice reported migraine with both tests, while 36% reported migraine after 1 of 2 tests [69]. The clinical trials evaluating aerobic exercise in migraine patients, in Table 4.2, did not report exercise-triggered attacks. Some screened patients for history of exertion-triggered headache and others for a history of exercise. Before initiating an exercise prescription, screening for a history of exercise-triggered headaches and considering alternative therapies first can help reduce the risk. Those that accept the risk should be counseled to avoid exercising at the same time as they are exposed to other known triggering factors [69].

Additional measures can be taken to reduce the likelihood of triggering a migraine with exercise. Eating before exercise can help avoid hypoglycemia due to prolonged endurance training; not eating is a common trigger of migraines [65, 67]. Staying hydrated during exercise may also help.

Evidence for Exercise in Tension-Type Headache and Cervicogenic Headache

Although the pathophysiology of tension-type headache (TTH) is poorly understood, it is frequently associated with pericranial tenderness on palpation as well as neck pain [70]. These muscular contributions are probably key to its mechanisms. TTH patients may have weaker muscle strength in neck extension, with a lower extension/flexion ratio [71]. These factors have led to the practice of strength training for the treatment of TTH, which is supported by several clinical trials.

Low-load endurance craniocervical and cervicoscapular exercises have been investigated for the treatment of chronic and episodic tension-type headache [3]. The exercises, performed under the guidance of physiotherapists, are a slow and controlled craniocervical flexion against resistance over time to train muscular control of the region. A circular latex band is used with one side positioned at the craniocervical region of the neck and the other fixed somewhat above the horizontal such that a sitting patient can perform slow and controlled craniocervical flexion. A RCT showed that adding low-load endurance exercises, 10 min twice a day for 6 weeks in addition to physiotherapy (massage, joint mobilization, posture work), was superior to physiotherapy alone for improving headache frequency [72]. Strength training was further assessed in another RCT that compared strength training to ergonomic and posture correction control [73]. Strength training was achieved with four shoulder exercises, with relative load progressively increased from 12 repetitions at 70% maximum intensity to 8 repetitions at 80% of maximum intensity. The number of sets was gradually increased, beginning with two sets per exercise and then three sets per exercise, three times per week. The exercises included shoulder abduction, shoulder elevation/shrug, rowing movement, and horizontal shoulder abduction with an elastic band for resistance. This trial showed a statistically significant reduction in headache frequency and duration, but clinically significant 30% or more reduction was not met, and no difference was seen between strength training and ergonomic and posture intervention. Better response to strength training was observed in patients with frequent episodic TTH compared to chronic TTH.

Patients with chronic TTH may benefit from strength training for neck and shoulder muscles in addition to aerobic exercise and stretching. Compared to episodic TTH, patients with chronic TTH have significantly more cervical myofascial trigger points, restricted neck mobility, and greater flexor head posture [74]. In a therapeutic clinical trial, patients were randomized to multicomponent exercise, acupuncture or relaxation training, and stress coping therapy. Similar outcomes were achieved with all interventions [75]. The exercise program consisted of 25 sessions, performed two to three times per week. At least eight training sessions were carried out under the supervision of a physiotherapist. Each training session began with 5–10 min of ergometric bicycling followed by five exercises focusing on neck and shoulder muscles, repeated 35 times and 3 sets of each (105 times total), with rest for 1–2 min between each exercise. The home exercise program consisted of similar exercises but fewer repetitions. Headache intensity reduced from a mean of 22 to 14.66 at 6-month follow-up, while headache-free days increased from 0.97 to 1.66. Another chronic TTH RCT compared manual therapy to usual care with a general

practitioner. Manual therapy consisted of mobilization of the cervical and thoracic spine, postural correction, and exercises used for the management of cervicogenic headache. After 8 weeks, the frequency of headaches was reduced by −6.4 days compared to controls [76].

A referral to physical therapy should be considered for chronic TTH patients for evaluation of neck mobility and posture and for a craniocervical muscle exercise prescription. Efficacy of interventions used by physiotherapists for TTH was gauged in a meta-analysis, and a statistically significant reduction in headache intensity (−1.11 on 1–10 visual analog scale) was found [56]. A combination of treatments such as physiotherapy, mobilization, craniocervical muscle exercise, and trigger point therapy was used in eight trials included in this analysis.

Cervicogenic headache is caused by nontraumatic disorders of the cervical spine and soft tissues of the neck resulting in head pain that can be made worse with provocative maneuvers of the neck and is frequently associated with neck pain. When cervical myofascial pain is the cause of headache, the headache may be more closely related to TTH.

The efficacy of various exercise programs for cervicogenic headache is difficult to assess. Because of the high prevalence of neck pain in patients with TTH and migraine [62], studies frequently combine patients with cervicogenic headache and TTH or focus on patients with neck pain and headache. A meta-analysis of several trials supports the role of a combination of physiotherapy, including craniocervical and cervicoscapular exercise, manual therapy, and mobilization for reduction of frequency and duration of cervicogenic headache [56]. An exercise program of (1) craniocervical flexion exercise targeting deep neck flexor muscles to address impairment in neck flexor synergy, (2) training of muscles of the scapula using inner range holding exercises of scapular adduction and retraction, (3) postural correction exercises performed through the day, and (4) isometric exercises using low-level rotary resistance to train neck flexors and extensors was performed for 6 weeks and was found to be more effective than control in reducing headache frequency and intensity [77].

Yoga has been used for the treatment of lower back pain and has been found to be helpful for patients with neck pain [78], and it may also be considered in the treatment of TTH. A meta-analysis with a single RCT of chronic TTH patients focusing on meditative yoga, as well as a mixed headache population, overall found statistically significant effect favoring yoga for reduction of headache frequency (−1.97), duration, and intensity. No benefit was observed for patients with migraine [79].

Post-Traumatic Headache

Mechanical force impacting the head can result in mild traumatic brain injury and headache that is notably associated with exercise intolerance. Mild traumatic brain injury, or resultant concussion, is a traumatically induced physiological disruption of brain function without structural damage. This disruption is immediately manifested by some of the following: transient confusion or disorientation or briefly impaired consciousness, brief amnesia surrounding the injury, and neurological

symptoms such as visual disturbance that may arise over minutes to hours [4, 80]. Longer-lasting post-concussion syndrome may consist of headache, along with visual disturbances, dizziness, impaired memory or concentration, sleep disturbance, difficulty with executive function, and change in mood. Headache is one of the most common sequelae of mild traumatic brain injury affecting up to 90% of patients [81]. Post-traumatic headache is a new headache, or significant worsening of a pre-existing headache disorder, starting within 1 week of the injury [70]. Symptoms can resemble migraine or TTH or other headache phenotypes [82].

Exercise intolerance, particularly bouts of intense physical activity in individuals with post-concussion syndrome and post-traumatic headache, has been long recognized. It presents a clinical challenge not only in athletes but in many patients who rely on physical activity at work or for management of stress and other health benefits [83]. Cerebral autoregulation disruption and autonomic system dysfunction are some of the underlying mechanisms of concussion [81, 84], which may explain why symptoms reappear or worsen with intense physical exertion. Subsymptom threshold aerobic exercise training, or exercise performed at an intensity below that which exacerbates symptoms, on the other hand, has been shown to help patients with concussion recovery. Though the exact mechanisms of the beneficial effects of graduated exercise on concussion recovery are not known, proposed pathways involve the autonomic nervous system and cerebral blood flow, as well as neuroplasticity [84, 85].

A protocol for subsymptom threshold aerobic exercise training consists of a baseline assessment of a threshold at which concussion symptoms, including headache, are exacerbated, followed by an aerobic exercise prescription that is limited to 80% of the threshold intensity. This protocol is outlined below, and derived from several clinical trials [85–89]. The exercise tolerance baseline test evolved from the Balke procedure for assessing cardiovascular health using a graded treadmill exercise and is now known as Buffalo Concussion Treadmill Test. This test is also clinically used to confirm post-concussion physiology and determine physiological recovery.

1. *Baseline assessment:* incremental treadmill exercise test according to the modified Balke protocol, or *Buffalo Concussion Treadmill Testing* [84, 87–90]. Contraindicated in patients with significant cardiovascular disease
   (a) On treadmill walk at 3.2 mph (for those 5´5˝ and under) and 3.6 mph (for those over 5´5˝) and 0-degree incline, such that patients are moving at a brisk walking pace
   (b) The incline grade is increased by 1° per min for the first 15 min while speed is maintained
   (c) At maximum incline of 15°, the speed is increased by 0.2–0.4 mph per min
   (d) HR measured continuously
   (e) Every minute, perceived exertion is assessed (RPE 6–20) as well as postconcussion symptom/headache severity
   (f) Test is continued until maximal exhaustion is achieved as defined by RPE > 18, or post-concussion symptoms recur or are exacerbated
   (g) HR_{max} noted at maximum intensity tolerated

If treadmill is not tolerated, cycling baseline assessment can be performed adapted from [86]

(a) On a recumbent stationary bicycle, cycle at low resistance setting, speed with low intensity with low perceived exertion (RPE of 11), for 5 min.
(b) At 5-min intervals, increase RPE intensity by one level until starting to experience an increase in symptoms or until a maximum of 30 min
(c) $Duration_{max}$ and HR_{max} noted

2. *Aerobic training prescription* [86, 90]

(a) Aerobic exercise can be performed 5–7 days per week
(b) Intensity is limited to 80% of HR_{max} for duration of 20 min, additional 5 min of warm-up and cooldown is to be performed, and activity is stopped if symptoms exacerbated
(c) If duration was used in baseline assessment, session duration is set to 80% $Duration_{max}$
(d) Reassess baseline every 1–2 weeks to readjust HR_{max} or $Duration_{max}$

Many clinical trials of physical activity after concussion implement a comparable subsymptom threshold exercise training program. A systematic review on rest and rehabilitation post-concussion concluded that, though there is some conflicting evidence, the majority of studies suggest a positive effect of subsymptom threshold aerobic exercise on decreasing time to recovery [90]. The 2017 International Conference on Concussion in Sport consensus statement suggests that after a sports concussion, a short period (24–48 h) of cognitive and physical rest should be recommended, followed by a closely monitored active rehabilitation program involving subsymptom threshold exercise [4].

Recently, several RCT confirmed that subsymptom threshold aerobic exercise with a prescription target 80% of heart rate or duration of exercise at which symptom exacerbation is seen is beneficial at reducing concussion symptoms, including headache. One multicenter RCT focused on the effects of aerobic exercise in early post-concussion recovery [89]. Adolescents having sustained a sports-related concussion within 10 days had a shorter duration to recovery of 13 days with aerobic exercise, compared to 17 days with stretching. Aerobic exercise consisted of daily stationary bike or treadmill (or walk/jog outside) at a prescribed heart rate of 80% of that at which symptom exacerbation was noted at a baseline assessment via the Buffalo Concussion Treadmill Testing. Exercise was performed for 20 min or stopped early if symptoms increased from pre-exercise symptom level. The control group was prescribed a 20 min daily stretching program that would not considerably elevate heart rate, and all interventions were initiated at least 48 h after injury. In another RCT, adolescents with prolonged symptoms after mild traumatic brain injury had a more significant reduction in post-concussion symptoms with subsymptom exacerbation aerobic training compared to full body stretching that was comparably timed and monitored [85]. Participants followed cycling baseline assessment protocol, as above, and after that did a 6-week training program, cycling 5–6 days per week at home at 80% of the duration that exacerbated symptoms. The

cycling test was repeated weekly to adjust the threshold that participants could tolerate.

The results of clinical trials and the consensus statement support recommendations to start physical activity early after mild traumatic brain injury for symptom reduction, in a graduated, subsymptom threshold, closely monitored program. Further, in our clinical experience, subsymptom threshold protocols can help patients with primary headache disorders, particularly chronic migraine. These patients frequently have low tolerability for aerobic activity, as well as many comorbidities that can benefit from regular physical activity. Though at this time there is no clinical trial data to support this recommendation, shared pathophysiology and symptoms between post-traumatic headache and migraine [82, 83] help support this treatment option.

Conclusion

Exercise has an important role in the treatment and prevention of headache disorders. In addition to aiding in recovery from post-traumatic headache, there is research supporting the prescription of aerobic exercise for the prevention of migraine and low-load endurance craniocervical and cervicoscapular exercise for tension-type headache. More research is needed to fill in the pieces of the pathophysiology puzzle linking the beneficial effects of exercise in specific headache disorders. There is a particular need for more investigation of aerobic and core strengthening exercise regimens for the prevention of chronic migraine as current data is limited and the demand for nonpharmacological treatment is unmet.

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Chapter 5
Obesity, Weight Loss, and Nutrition in Headache Disorders

Cynthia Emilie Armand

Introduction

Obesity, weight management, and nutrition are more often discussed in the setting of cardiovascular health; however, their relevance extends into various other bodily systems, including the nervous system. Primary headache disorders are inherent brain conditions not attributable to other bodily causes. The pathophysiology behind head pain is quite complex due to the underlying multifactorial mechanisms. However, there are factors, both intrinsic and extrinsic, which can contribute to the worsening of an already predisposed brain to further headache attacks. Controlling these factors can lead to better headache management and improved quality of life. This chapter will begin with an overview of obesity and the evidence supporting its connection to chronic daily headache (CDH). The impact of weight loss on headache will be reviewed through its association with body mass index. Next, a generalized overview of nutrition as a trigger to certain headache disorders will be discussed. Attention will be directed toward particular ingredients and diets speculated to play a part in headache control. Lastly, a review of the principal components of a diary and suggestions on how to perform an elimination diet for proper nutritional trigger identification will be presented.

Obesity and Its Link to Headache Disorders

Obesity is well-known to influence many illnesses, including heart disease, type II diabetes, stroke, and even certain forms of cancer. From 2015 to 2016, the Centers for Disease Control and Prevention reported the prevalence of obesity in the United

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States to be 39.8%, affecting close to 93 million American adults. In 2016, the World Health Organization reported the global prevalence of headache disorders to be 50%, with tension-type headache (TTH) being the most common. Researchers have found obesity to be a risk factor for CDH, those occurring ≥15 days per month [1, 2]. Furthermore, in research evaluating factors influencing the transition from episodic headache to CDH, researchers found obesity to increase the annual incidence of CDH by five times the rate of those with normal weight [2]. In another large population study, researchers found obesity to be a risk factor for increasing frequency and severity of chronic migraine (CM) [3], but not for migraine prevalence or chronic tension-type headache (CTTH) in general [4].

Although there are various bodies of research highlighting a positive correlation between obesity and headache disorders, there are also research studies showing a lack of association between the two [5]. One large study of middle-aged women did not consistently link migraine with an increased incidence of weight gain or obesity [6]. Another revealed no correlation between disability and severity of migraine and body mass index (BMI) [7]. Furthermore, Bigal et al. found that frequency and migraine prevalence were not associated with BMI [8].

Despite differences in study findings, there are various mechanisms, which may explain obesity's influence on headache frequency and occurrence. Obesity is a pro-inflammatory and pro-thrombotic state due to the secretion of cytokines by fat cells called adipocytes [4]. This pro-inflammatory process is furthered due to the high activity of macrophages within the adipose tissue itself [9]. In addition to the pro-inflammatory cytokines, certain peptides, such as calcitonin gene-related peptide (CGRP), are known to play a role in migraine pathophysiology and are present in the obese (primarily women) at higher levels. It is postulated that a diet containing increased fat intake may further increase CGRP circulation [10]. Other neuropeptides, orexin A and B, secreted by the hypothalamus, are active participants in the pain pathway through their influence on CGRP secretion [11, 12]. These neuropeptides are disrupted in states of obesity [13]. Therefore, Bigal and Lipton postulated that this disruption might lead to increased vulnerability to neurogenic inflammatory states, which can perpetuate cytokine release and contribute to increased migraine occurrence [4].

Few clinical trials have been conducted to determine if weight loss intervention positively impacts headache frequency and severity. One recent randomized, single-blind trial published in 2018 assessed change in migraine days per month in 110 women. All participants with a BMI of 25.0–49.9 followed either migraine education guidelines or a behavioral weight loss (BWL) intervention targeting exercise and eating behaviors for weight loss. Results showed no significant difference in migraine days per month among the two intervention groups, despite a more significant mean weight loss experienced by the BWL group [14]. In another study examining metabolic parameters that may influence migraine occurrence, 112 obese adolescents with migraine who had undergone a weight loss intervention program were evaluated for changes in bodily metrics in conjunction with migraine attack frequency. Obese adolescents who experienced migraine attack persistence had significantly higher weight, body mass index, and waist circumference. Furthermore,

adolescents with insulin resistance had 3.5 times the odds of having persistence of their migraine as opposed to those without insulin resistance [15]. Based on the data presented in this section, many neurologists and headache specialists continue to view weight loss as an additional factor that may supplement evidence-based approaches to headache management.

Dietary Trigger Identification

One of the motivating factors in a patient's search for headache freedom is the question of why a headache attack is occurring. Triggers are not the cause of headaches, as we know them, but rather the contributors to a headache attack. Triggers are what bring on attacks in individuals already predisposed to having them. Triggers come in multiple forms, including strong emotions, stress, weather changes, and fluctuations in sleep patterns. Nutrition has long been considered an integral component of triggering headache attacks, especially in people with migraine. Patients often turn to nutrition, because for many, the cause-effect relationship might be apparent.

In 2016, Martin and Vij outlined five categories of possible mechanisms of dietary triggers to headache disorders: (1) effects on neuropeptides, neuroreceptors, and ion channels, (2) inflammation, (3) cortical effect, (4) vascular effect, and (5) activation of the sympathetic nervous system [16]. These categories may provide answers to the most common questions many headache sufferers have regarding dietary triggers. Below is a review of the most common ingredients that may contribute to headache attacks through one of the five mechanisms described above.

The Most Common Dietary Triggers

Chocolate

Chocolate is a common anecdotally reported headache trigger seen in clinical practice. Two to twenty-two percent of individuals with migraine have self-reported chocolate to be a trigger [17]. In various diary-based studies, chocolate as a headache precipitant has been seen in only a minority of individuals. In Park et al.'s electronic diary study investigating potential triggers of episodic migraine, chocolate was one of the least reported triggers compared to other non-food triggers. However, chocolate intake was more so present on days of migraine attacks [18]. Provocation studies do show an association between chocolate and the precipitation of headache, but do not reach statistical significance. In a chocolate vs. placebo provocation study, 42% of subjects given chocolate experienced migraine, as opposed to 0% in the placebo group [19]. Another study, a double-blinded crossover provocation study, compared chocolate intake to carob intake among 81 female participants with chronic recurrent headache [20]. Headache did occur in both groups with no

significant difference (22.7% in the chocolate group vs. 20.5% in the carob group; $p < 0.68$). From the above studies, one cannot ignore chocolate as a possible trigger to headache, despite the conflicting evidence revealed in available studies.

The idea of chocolate as a trigger has indeed been challenged since food cravings are part of the premonitory phase of a migraine attack. Charles discusses the involvement of the hypothalamus in the premonitory phase of a migraine attack, which fits well since the hypothalamus plays a part in appetite [21]. Positron emission studies also show hypothalamic activity during this phase of the migraine attack [22]. Are individuals with migraine already at the first stage of their attack when they eat chocolate due to increased appetite and cravings? Or is chocolate intake triggering the phases to begin? More studies are needed to answer these common questions.

If we lead with the notion that chocolate is indeed a trigger for some, various mechanisms have been proposed to support this assertion. Two examples of this are processes that involve serotonin and nitric oxide. Serotonin is known as a significant neurotransmitter in migraine pathophysiology. While one study found that chocolate contains elevated levels of serotonin, no concrete evidence seems to solidify the theory that increasing chocolate intake, which would potentially increase serotonin levels, would trigger a migraine attack [23, 24]. Though the theory of vasodilation and its relation to migraine onset has been challenged over time, studies have shown chocolate to have a link to nitric oxide (NO), a potent vasodilator. There are a few studies that reveal the effect of cocoa flavonoids increasing levels of NO; however, others show that they may lower NO levels by reducing the production of NO synthase [25–27]. This relationship with migraine pathophysiology remains conflicting.

Just as chocolate has been speculated to trigger migraine attacks, it has been shown to potentially have a hand in migraine prevention. In their review of chocolate and migraine, Nowaczewska et al. point to various studies that demonstrate chocolate's plausible beneficial effect on migraine via its role in increasing magnesium, riboflavin, and serotonin concentrations, suppressing nitric oxide levels, and inhibiting CGRP release [28]. The migraine-chocolate relationship is indeed conflicting. More research and individualized approaches to evaluation and care are necessary.

Gluten

Gluten is a type of protein found in certain starchy foods. Dietary gluten hypersensitivity exists in many forms, one of which, celiac disease, is an autoimmune condition diagnosed by clinical history, serum testing, and intestinal biopsy. Many individuals with headache disorders are often curious about the relationship between gluten and headache occurrence. There have been various studies examining the relationship between celiac disease, migraine, and the effect of a gluten-free diet on both conditions simultaneously. In one review and meta-analysis published in 2018, researchers evaluating the relationship between celiac disease and headache found a 22% and 18% mean pooled prevalence of headache occurrence in celiac-positive

adult and pediatric populations, respectively, mostly being of migraine semiology. Based on their results, they suggested that individuals with headache disorders be screened for celiac disease since up to 75% of patients with celiac disease showed near-complete resolution of headaches when treated with a gluten-free diet [29]. In another study published in 2015, 100 patients with celiac disease were compared to 100 patients with reflux esophagitis in the absence of celiac disease. The celiac disease group showed 2.5 times more migraine attacks. After implementing a gluten-free diet, 25% of celiac disease patients experienced cessation of migraine attacks, while 38% had a reduction in migraine frequency and severity [30]. The relationship between headache and gluten in the absence of gluten insensitivity and celiac disease has not been fully elucidated. Further studies are needed to examine a definitive cause and effect relationship.

Monosodium Glutamate

Glutamate is the primary excitatory neurotransmitter of the nervous system. Many studies have revealed glutamate's involvement in migraine pathophysiology, which include propagation of pain signals, nerve hyperexcitability, and cortical spreading depression. As a result, glutamate receptors have long been a target for migraine therapy [31].

Monosodium glutamate (MSG) is a sodium salt comprised of sodium and glutamic acid. It is mostly found in processed foods such as seasoning salts, canned goods, and certain condiments. It is well-known to be a common ingredient of Chinese take-out dishes, so much so that "Chinese restaurant syndrome," characterized by palpitations, headache, paresthesias, flushing, and sweating, was first described as an effect of ingesting MSG-containing Chinese food [32]. MSG, as a provoking factor of headache, was discussed in a systematic review of studies investigating Chinese restaurant syndrome [33]. High MSG levels dissolved in liquids did show evidence as a headache trigger, whereas MSG added to foods did not.

Aspartame

Aspartame is a non-saccharide artificial sweetener, often used as a sugar substitute. Newman and Lipton described two patients with headaches after taking the migraine rescue medication rizatriptan in a disintegrating formulation, which contains aspartame [34]. Various crossover studies have also examined the relationship between aspartame and headache onset. Two crossover studies revealed a significantly higher frequency of migraine attacks after the ingestion of aspartame tablets as compared to placebo tablets [35, 36]. However, two other crossover provocation studies failed to show similar results. One study compared high aspartame intake to low aspartame intake, neither of which showed a difference in headache incidence [37]. The

other study failed to show a difference in headache provocation with aspartame versus placebo administration in 40 study participants who had previously reported triggering of headaches from aspartame-containing foods [38].

Histamine

Histamine is a biogenic amine known to play a role in the pathophysiology of migraine through its involvement with neurogenic inflammation [39]. Several foods containing high levels of histamine include nuts, smoked meats, and shellfish. Ingestion of these types of foods has not only been shown to induce headache but has also resulted in a described histamine intolerance syndrome marked by headache, wheezing, pruritus, hives, or flushing [17]. Given histamine's role in migraine, research has focused on how histamine impacts the nervous system in the hopes of finding future pharmacologic targets with the potential of decreasing migraine frequency and severity. Four histamine receptors have been revealed: H1, H2, H3, and H4 [39, 40]. Receptor H3, in particular, has a higher affinity for histamine, and with its activation, there is decreased release of histamine, allowing for anti-nociceptive effects [39]. Therefore, histamine presents a potential pharmacologic target for migraine. Though avoidance of histamine-containing foods can potentially lead to improvement of migraine, future studies are needed to explore this treatment route in addition to the pharmacologic exploration of the histamine receptors.

Nitrites

Nitrites work as preservatives and are often found in cured meats, sausage, or hot dogs. They prevent the growth of certain bacteria such as *Clostridium botulinum*, a harmful neurotoxic microbe. In a 1972 case report, Raskin and Henderson first described nitrites as a possible migraine trigger in a patient experiencing headaches after eating nitrite-containing foods [41]. Since then, nitrites have consistently been speculated to be among the common food ingredients contributing to headache attacks.

Tyramine

Tyramine is a naturally occurring amine found in certain foods and drinks such as aged cheeses, fermented meats, and wine. Tyramine is broken down by monoamine oxidase; therefore, in individuals who are prescribed monoamine oxidase inhibitors, careful attention must be paid in regard to avoidance of tyramine-rich foods.

The inability to break down tyramine leads to elevated serum tyramine levels, resulting in a hypertensive crisis, of which symptoms include malignant hypertension and severe headache [42]. Following Blackwell et al.'s study, which showed an initial association between tyramine and headache precipitation due to systemically high levels of tyramine, multiple studies have inconsistently shown tyramine to be a valid trigger of headache disorders. However, one study in 2013 did reveal elevated levels of tyramine in patients with CM in comparison to patients with alternate headache diagnoses and those without headache [43].

Caffeine

Caffeine is often used as a form of acute therapy for headache attacks, perhaps due to its ability to promote blood vessel vasoconstriction as well as inhibit leukotriene and prostaglandin synthesis and further improve absorption of alternative analgesics [44]. However, prolonged caffeine use has been shown to impact headache disorders by worsening headache attacks, creating a caffeine withdrawal headache, and eventually leading to medication overuse headache [44]. The vascular effect occurs in caffeine withdrawal headaches when adenosine receptors, usually competitively antagonized by caffeine, become hypersensitive after chronic caffeine use. With abrupt caffeine cessation, those adenosine receptors become readily available, leading to increased cerebral vasodilation, contributing to a caffeine withdrawal headache attack [45]. Increased caffeine consumption precipitates medication overuse headache by enhancing cortical hyperexcitability, followed by increased glutamate release [46]. An excitatory cascade eventually causes enhanced release of neuropeptides, such as CGRP, which have been identified to play a significant role in migraine pathophysiology. The above hyperexcitability also influences caffeine's ability to worsen primary headache disorders [44].

Alcohol

Alcohol has long been considered a headache trigger. Dueland et al. explained this as a more common occurrence for migraine and cluster headaches [47]. In Davis-Martin et al.'s review and meta-analysis of alcohol and its relation to primary headache disorders, 22% of those with migraine or tension-type headache noted alcohol as a trigger. In terms of specific alcohol type, red wine was three times more likely to be a trigger than beer [48]. Panconesi pinpoints the influence of subcortical pain modulatory circuits on central pain pathways as a plausible mechanism in the triggering cluster of migraine attacks [49]. Aside from alcohol itself, alcoholic drinks contain other possible relevant chemicals, which can serve as migraine triggers. In red wine, for example, there is evidence for the presence of flavonoid phenolic

compounds and 5-hydroxytryptamine as migraine triggers. However, other red wine components such as tyramine, phenylethylamine, and sulfites require more consistent correlations to establish a concrete cause-effect relationship [50].

How to Identify Dietary Triggers

Keep a Food Diary

Maintaining a general food diary with simultaneous inputs of headache attacks is the first step of a nutritional evaluation for headache correlation. Through this bookkeeping method, patterns arise that may point to particular food-triggered headache attacks. The focus should initially be placed on keeping a general dietary account. If headache attacks do occur in relation to specific food intake, then further in-depth diary accounts should be made, such as including particular ingredients.

Because keeping a food diary can be a harrowing task, the following basic steps, summarized in Table 5.1, may be followed to maintain consistency and accuracy.

1. *Initial dietary record keeping should be simple*. Aim to keep a general account of meal, snack, and beverage intake. Do not initially focus on individual ingredients.
2. *Record time of nutritional intake*. In addition to timing correlation to a potential headache attack, the timing of nutritional intake is critical to assess whether delayed intake or skipping meals presents as a possible trigger. Timing of a headache attack related to specific food intake may also vary, as attacks may not always occur on the same day a triggering food or beverage was consumed.
3. *Record specific ingredients after 1 month*. After the initial record keeping of a diary for about 1 month has occurred, fine-tuning with the inclusion of ingredients should occur. The suggestion of including this into diary input after a month of record keeping serves to ease into what most would believe to be a burdensome portion of bookkeeping. This 1-month time frame suggestion may even occur earlier if a particular food with multiple contributing ingredients is identified. The timing of individual ingredient identification is at the discretion of the diary keeper.
4. *Record potential confounding trigger contributors*. Nutrition is not the only potential trigger of headache disorders. Other contributors include menstrual cycle, temperature and weather changes, barometric pressure fluctuations, acute illness

Table 5.1 Key components to a nutritional diary

Keep initial dietary accounts simple
Record timing of nutritional intake
Hone into specific ingredients after baseline diary accounts are specific
Record headache occurrence
Record potential confounding non-dietary triggers

(i.e., common cold/flu), and sleep-wake cycle fluctuations. Keeping a record of the above mentioned alternate triggers allows for the identification of confounders when fine-tuning nutritional cause and effect on the attack day in question.

Template for Data Recording

Figures 5.1 and 5.2 reveal general templates that may be used for food and headache diary record keeping. Diaries can be as simple as writing down certain foods eaten while simultaneously noting headache occurrence on a single page or creating a grid for easily visualized interpretation of data recorded. Figures 5.1 and 5.2 are simply examples to visualize integral components. In the age of smartphones and electronic advancements, various diary applications have emerged, which allow for ease of the process. Many patients who are digital savvy do find the smartphone diary applications the most seamless since several also include record keeping of the possible confounders previously mentioned.

Date: 01/10/2020	Weather: Cloudy, 37°F		
Meal (Time)	Food Description	Beverage	Headache Occurence
Breakfast 8:45AM	Oatmeal/chia/ Almond Milk Blueberries	Ginger Tea	None in AM
Lunch			
Dinner			
Snack 1			
Snack 2			

Fig. 5.1 Sample nutritional diary

Day	1	2	3	4	5	6	7	8	9
Morning			x	x	x	x			
Noon				x	x				
Evening				x	x				
Menstruation				x	x	x	x	x	x

Fig. 5.2 Sample headache diary

Dietary Trigger Elimination

Elimination diets require the identification of provocative foods, beverages, or ingredients followed by elimination from the diet. Patients may notice that a migraine attack occurs upon exposure to a clear dietary trigger. In this case, avoidance of that particular trigger can be recommended. For most, however, it is difficult to establish a clear association between dietary triggers and headache. It is here that a food diary can be helpful. After data is recorded, the patient, along with the help of a healthcare professional, should review it to identify critical associations, which may exist between foods and headache occurrence. After a particular food trigger is identified, it is then suggested to stop its intake for about 3–4 weeks. During these 3–4 weeks, a food and headache diary should be maintained to monitor for worsening or improvement of headache attacks. After this time, that same food should be reintroduced into the diet, and the diary should be continued to monitor the impact on headache frequency and severity.

There are several issues with using a food diary to guide an elimination diet. The trigger-effect relationship between food and migraine may depend on the quantity of food consumed: a small amount of a food ingredient may not trigger an attack, but a more considerable amount might. Additionally, certain foods may not necessarily trigger a migraine attack with every exposure; this inconsistency could make identification of that food as a trigger a dilemma. Furthermore, the timing of a migraine attack in relation to food intake may vary from immediate onset upon ingestion to delayed onset, stretching from 24 to 48 h after ingestion. Alternatively, other unpredictable environmental factors such as weather, barometric pressure, and sleep-wake cycle disruptions can serve as triggers to a migraine attack; a look into these potential triggers should be considered, especially if food monitoring yields little in return. For all the above reasons, the subjective measure of food trigger identification can be particularly challenging.

Perhaps a better way to embark upon an elimination diet is to use serological testing to identify foods to be eliminated. IgG can be a marker for foods that cause inflammation and trigger migraine attacks in predisposed individuals. In their randomized control trial of 167 participants in which foods containing IgG antibodies were excluded, Mitchell et al. found a 1-day reduction in headache days at 4 weeks [51]. Alpay and colleagues, in their randomized control trial of 30 participants with migraine,

effectively demonstrated that avoiding foods with IgG antibodies can significantly reduce headache frequency. Participants excluding IgG foods had a 3-day reduction in headache days as compared to the lack of change in headache days by participants with migraine who ate foods with IgG antigens [52]. Moreover, Adyinlar et al.'s randomized trial evaluated baseline migraine attack characteristics in 21 patients with migraine and irritable bowel syndrome who either followed an IgG elimination diet or an IgG-positive diet. Results revealed significant reductions in migraine frequency, severity, and duration for the IgG elimination diet, but no change in the IgG-positive diet [53].

Specific Diets and Their Influence on Headache Disorders

In patients without clear food triggers or in those with comorbid medical conditions, a more specialized diet may be considered. The common theme shared by these diets is that, rather than fixating on a particular ingredient type, the focus is on regulation, reduction, or complete elimination of specific food groups. We will now examine the most common diets currently circulating with these themes.

High- and Low-Sodium Diets

Per the US Food and Drug Administration, a low-sodium diet refers to a daily value of 5% or less of sodium per serving; a high-sodium diet contains a daily value of 25% or more [54]. Sodium is often thought to play a role in headache onset; however, studies conducted to examine its influence on headache disorders have been controversial due to conflicting results. Amer et al. performed a randomized multicenter trial in which participants diagnosed with prehypertension were asked about headache onset while either following the DASH (Dietary Approaches to Stop Hypertension) diet or a control diet in which sodium intake was not regulated. Those with prehypertension on the DASH diet at low sodium levels experienced a lower frequency of headache attacks at 36% as opposed to a higher frequency of 47% experienced by those on the control diet with high sodium levels [55]. In another study, Pogoda et al. looked into whether there was an association between severe headache or migraine and dietary intake. They performed a 1-day interview of dietary intake and asked participants whether or not they had experienced a severe headache or migraine in the previous 3 months. There was an inverse relationship between sodium intake and severe headache or migraine occurrence; this inverse relationship was only statistically significant in women with a lower BMI (less than 50th percentile) [56]. Martin et al. speculated that differences in study design might have contributed to the varying results of these two studies [16]. Blitshteyn explained that the inverse relationship seen between salt intake and migraine occurrence is justified by the underlying pathophysiology known to be present in individuals with migraine and often comorbid autonomic disorders such

as POTS (postural orthostatic tachycardia syndrome). In these autonomic disorders, the main contributor to symptom manifestation is the finding of hypovolemia. Treatments targeted toward treating hypovolemia (via plasma volume expansion) are cornerstones of symptom control. These treatments, such as low dose beta-blockers and fludrocortisone, while improving autonomic dysfunction, can simultaneously improve migraine control.

Additionally, treatments geared toward migraine control can also improve autonomic dysfunction. The potential of this dual improvement using a singular treatment is perhaps evidence of a shared pathophysiologic mechanism. Blitshteyn elaborates on this further, purporting that individuals with low salt intake have a lower plasma volume (this also is more so in women with lower BMI as evidenced by lower blood pressure readings), and this lower plasma volume can work as a trigger to cerebral vasculature leading to a migraine attack. Therefore, through this pathophysiologic mechanism, there is plausibility in a high-salt diet leading to decreased migraine frequency [57].

High-Folate Diet

In their review of headache and diet, Martin and Vij proposed that certain patients with migraine might benefit from a high-folate diet or supplementation with folate, vitamin B6, and vitamin B12 [16]. The benefit of these vitamins for migraine is possibly due to their role in the metabolism of homocysteine, a major protein involved in blood and vascular health. Folate, vitamin B6, and vitamin B12 serve as cofactors, which allow for the conversion of homocysteine into alternate forms essential for protein function. An enzyme called methylenetetrahydrofolate reductase (MTHFR) allows for folate availability. The MTHFR gene, mainly the T allele of the MTHFRC677T polymorphism, is significantly associated with migraine with aura and a more severe disease phenotype with higher levels of homocysteine [58]. In a study comparing controls to individuals with migraine with aura, the migraine with aura group was shown to have higher levels of homocysteine in cerebrospinal fluid [59]. A recent case-control study of 140 participants (70 with migraine vs. 70 without) showed that individuals with low vitamin B12 levels and high methylmalonic acid levels have a higher likelihood of developing migraine [60]. In a randomized, double-blind, placebo-controlled trial published in 2009, 52 patients diagnosed with migraine with aura received 6 months of either daily supplementation with 2 mg of folate, 25 mg of vitamin B6, and 400 mg of vitamin B12 or placebo. As a result, the treated group showed statistically significant reductions in serum homocysteine levels and reduced prevalence of migraine disability, as well as headache frequency and pain severity [61]. Given the pathophysiologic correlation and above evidence, there is promise in utilizing folate and vitamin B12 supplementation in headache disorders, specifically migraine with aura.

Low-Fat Diet

Given the previously discussed evidence existing between weight reduction and headache disorders, it is natural to surmise that a low-fat diet may produce similar results. An open-label study conducted in the late 1990s revealed that intervention with a low-fat diet significantly reduced migraine attack frequency, severity, duration, and rescue medication intake [62]. In this study, 54 adults with migraine commenced with a baseline 28-day account of dietary intake and migraine attack frequency characteristics. They were then asked to restrict lipid intake to no more than 20 g/day for 28 days. Fifty-one of the 54 subjects reported a >40% improvement in headache index, and 35 subjects reported an improvement of 85–100% [62]. In a 2015 crossover trial by Ferrera et al., 63 participants with episodic or chronic migraine were assigned to a low-lipid diet (<20% of total daily energy intake) or a normal lipid diet (25–30% of total daily energy intake) for 3 months. The frequency and severity of migraine attacks decreased significantly in the low-lipid intake group [63]. These studies show preliminary evidence that a low-fat diet may be beneficial for migraine management. More extensive randomized placebo-controlled trial studies are needed to solidify this relationship.

High-Omega-3 and Low-Omega-6 Fatty Acid Diet

The pathophysiology of migraine is thought to involve the active participation of inflammatory cytokines, which propagate pain signaling. Since omega-3 fatty acids have proposed benefits in various disorders due to their anti-inflammatory properties, they may be a non-pharmacologic alternative for migraine treatment. The primary fatty acids used by the nervous system are the long-chain polyunsaturated fatty acids, which consist of omega-3 and omega-6 fatty acids. Omega-3 fatty acids are essential components of cell membrane structure and include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [64]. As observed in rat studies, omega-3 fatty acids naturally work to decrease the production of specific inflammatory proteins and interfere with the function of others [64]. One study investigated the role of omega-3 fatty acids in migraine. The use of omega-3 fatty acids (in the form of fish oil) plus valproic acid was compared to valproic acid alone. This study found that the addition of omega-3 fatty acids led to a significant decrease in migraine frequency, duration, and severity [65]. Another study showed that patients with migraine using 1 g of omega-3 fatty acid supplementation alone reported both a decreased frequency and a 74% reduction in headache severity [66]. Moreover, Sanders et al.'s cross-sectional study published in 2018 showed that high dietary intake of long-chain omega-3 fatty acids EPA and DHA was associated with a lower prevalence of headache attacks among US participants with the strongest association existing for non-Mexican Hispanics [67].

While omega-3 fatty acids have been shown to exhibit anti-nociceptive properties, omega-6 fatty acids have been pro-nociceptive [68]. In a 2013 randomized clinical trial, researchers evaluated the relationship between omega-3 and omega-6 fatty acids and their relationship with nociception. The dietary intervention of a strict high-omega-3 and low-omega-6 fatty acid was compared to low-omega-6 intake alone. The intention-to-treat analysis revealed a statistically significant reduction in headache days per month, 8.8 days, in the high-omega-3 and low-omega-6 group. This group additionally showed a reduction in headache duration by 4.6 h. Anti-nociceptive markers were also higher for this group [69]. These studies are further evidence of the potential benefit of a high-omega-3 fatty acid/low-omega-6 fatty acid diet in the management of headache disorders.

Ketogenic Diet

The ketogenic diet (KD) focuses on high-fat, low-carbohydrate, and moderate-protein intake. Carbohydrates are typically restricted to <20 g/day. This diet has been touted to promote rapid weight loss. During the natural fasting state, the body transports fatty acids to the liver, turning them into ketones. Ketones are then transported to various bodily organs and converted into glucose for use as fuel. Weight loss via the ketogenic diet uses the above mechanism as an ongoing process by putting the body into a state of ketogenesis. Fat stores are used as fuel via gluconeogenesis, the conversion of non-carbohydrate sources, and fat becomes the body's primary source of energy, mainly in highly metabolic tissues, namely, the heart, brain, and skeletal muscle.

Since the early 1900s, ketones have been recognized and used in intractable epilepsy management. Since epilepsy is marked by neuronal hyperexcitability, ketosis is believed to impact this condition by enhancing the production of gamma-aminobutyric acid (GABA), the primary inhibitory neuron of the central nervous system [70]. Likewise, in migraine, it is thought that ketosis may attenuate headache severity by increasing GABA to decrease brain hyperexcitability [71]. Ketosis may decrease CGRP synthesis and release and impede cortical spreading depression [72]. Additionally, ketosis may prevent neurogenic inflammation by downregulation of pro-inflammatory substances such as cyclooxygenase, prostaglandins, and tumor necrosis factor-alpha [73].

Five non-randomized prospective open-label studies have been conducted to evaluate the utility of a KD in migraine. The earliest study was done in 1928 and assessed the effect of the ketogenic diet in 18 adults with migraine. Half of the studied patients reported headache improvement [74]. In a 1930 study by Barborka, 50 adults with refractory migraine were placed on a ketogenic diet for 6 months. Seventy-eight percent of patients benefited from the diet, with 28% achieving complete remission [75]. Since then, there have been few studies addressing the effect of a KD on migraine. In a 2013 and 2015 study, adults with migraine on a ketogenic diet for 1 month saw a reduction in headache frequency [76, 77]. The most recent study, done in 2016, showed significant improvement in the frequency and duration of migraine attacks after 1 month of a KD [78].

While the evidence is limited, it is possible for ketogenesis to positively impact migraine. If this is to be considered, a careful preliminary medical evaluation should occur to assess if KD is a safe option. If KD is deemed appropriate, close supervision by a medical professional well-versed in ketogenesis and its effects should occur to ensure a proper and safe diet protocol.

Low Glycemic Diet

In a low glycemic diet (LGD), daily carbohydrate intake is restricted to 40–60 g with a glycemic index (GI) of less than 50 relative to glucose [79]. In LGD, carbohydrates mainly come from fruit, vegetables, legumes, and high-fiber cereals. This diet can be effective in weight, diabetes, and hyperlipidemia management. It is postulated that LGD may modify the inflammatory response.

In a randomized control trial by Evcili, 350 adults with migraine were assigned to a LGD group or a prophylactic medication group (receiving propranolol, flunarizine, amitriptyline). After 1 month, migraine attack frequency reduced significantly in both groups. After 3 months, there was a significant reduction in headache intensity in the LGD group [80]. There have been no other studies specifically examining the effect of LGD in migraine. Thus, while a LGD diet may be beneficial for migraine, additional studies are needed.

Hydration Versus Dehydration

Water intake has long been a lifestyle modification recommendation by headache specialists. Spigt and colleague's randomized control trial revealed that drinking 1.5 L of water per day could improve the quality of life of individuals with recurrent headaches [81]. Moreover, there have been several studies demonstrating improvement of migraine attacks with water intake and worsening of headache occurrence with lack of water ingestion [82–84]. However, there is a lack of large randomized control trials specifically evaluating dehydration as a migraine trigger and hydration as an effective means of migraine prevention.

Dietary Consistency

Headache specialists have always recommended consistency in dietary intake as one of the lifestyle factors to help manage the frequency of migraine attacks. The origin of this advice is from Critchley and Ferguson's 1933 statement that a missed meal and exercising on an empty stomach may cause an attack [85]. Thirty-three years later, Blau and Cummings performed research that showed that 6 out of 12 migraine patients developed a migraine attack after fasting for 11–14 h; the blood sugar levels recorded showed lowest values to be 44–77 mg/

mL [86]. The idea that dietary consistency would prevent hypoglycemia and prevent migraine attacks seems plausible. However, there has not been research showing a robust and consistent correlation. Finkel et al. explained that consistency in diet had been evaluated through the observance of specific dietary components and consistent avoidance of potential triggers. Whether or not a consistent diet plays a role in migraine can be answered by taking into account the complex interplay between the migraine brain state, which is susceptible to attacks at any time, the impact of specific food ingredients that can trigger an attack, and the understanding of the inflammatory neural tissue response to dietary influences [87]. This will better inform researchers on how to conduct future studies on dietary consistency, which will lead to improved patient counseling and treatment.

Clinical Approach to Diet

The first step for most patients is to avoid recognized food triggers. Next, the choice of a specific diet should be individualized to the patient, with special attention paid to comorbid factors and headache type. Figure 5.3 reviews this clinical approach. For obese patients with headache, consider a diet focused on weight loss such as a low-carbohydrate or low-fat diet. Headache patients with clinical clues suggestive of celiac sprue or nonceliac gluten sensitivity (diarrhea, ataxia, peripheral neuropathy, history of autoimmune disorders) may benefit from a gluten-free diet. Such persons should be screened with IgG and IgA antibodies against transglutaminase and gliadin. If positive for one or more of these antibodies, they might consider following a gluten-free diet. A low-histamine diet can be considered in those with symptoms of histamine intolerance on the ingestion of food (e.g., flushing, diarrhea, wheezing, urticaria, or rhinitis). Patients with migraine with aura can be tested for the MTHFR gene mutation. Those with the C allele of the MTHFR gene mutation might benefit from a high-folate diet or a supplement that contains folate (2 mg), vitamin B6, and vitamin B12.

If there are no specific comorbid medical disorders to guide the choice of a diet, then consider a high-omega-3/low-omega-6 diet, low-fat diet, or elimination diet of IgG-positive foods. These three diets have the highest level of evidence. Of note, it may be necessary to employ two or more dietary interventions in patients to see an optimal response.

Conclusion

Headache disorders are complex conditions that are impacted by various intrinsic and extrinsic factors. Obesity is a risk factor for chronic daily headaches; however, BMI studies are inconsistent in providing support for weight loss contributing to headache control. Anecdotally, various aspects of nutrition have also been

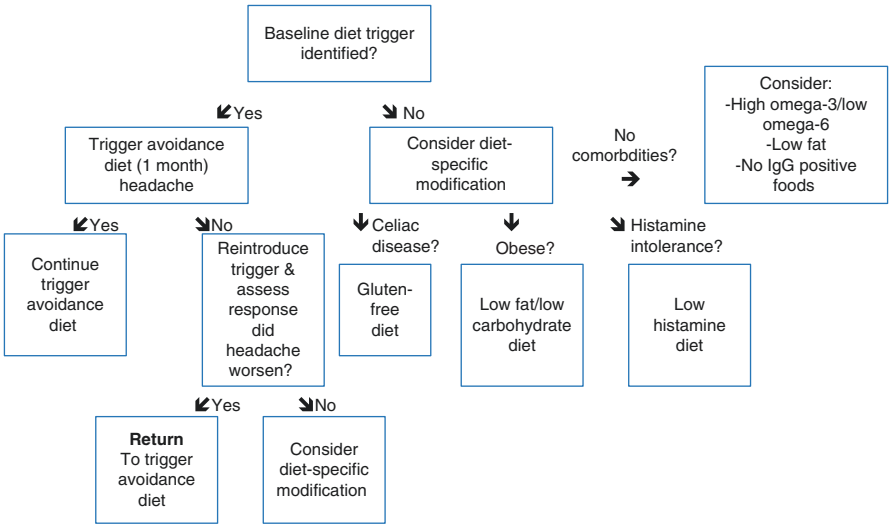

Fig. 5.3 Approach to diet algorithm

speculated to have a connection with headache occurrence. For more commonly reported ingredients such as chocolate and gluten, studies show supporting and refuting evidence for triggering headache attacks. However, for others, namely, nitrites and alcohol, a more consistent correlation is shown.

A joint food and headache diary is the most important first step to identifying food ingredients as triggers in headache attacks. An individual's bodily make-up differs from the next, and a trigger for one person may not be a trigger for another. Diaries should begin with a simple account of baseline behavior and can then evolve to include greater detail. Patients and their healthcare professionals should review the food diary together to identify critical associations. If a particular food is identified as a trigger, it can then be temporarily eliminated from the diet with close symptom monitoring.

For many, however, it is difficult to identify clear food triggers. In these individuals, consider a more specialized diet that focuses on regulation, reduction, or complete elimination of specific food groups or ingredients. Despite study limitations such as small sample size and lack of blinding, the three diets with the most promise with respect to efficacy include the high-omega-3/low-omega-6, low-fat, and IgG-positive food elimination diet.

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Chapter 6
Headache and Sleep

Joseph A. Diamond and Lauren R. Natbony

Introduction

Sleep is an essential biological function and a highly conserved behavior across animal evolution [1]. During sleep, most of the body's systems are in an anabolic state, which helps restore the immune, nervous, and muscular systems. Sleep maintains mood, enhances memory and cognitive function, and supports the endocrine and immune systems [2]. Humans spend approximately one-quarter to one-third of their lives in the active state of sleep, allowing a considerable opportunity for overlap between normal sleep, sleep disorders, and headache.

Sleep disorders occur in an estimated 50% of individuals with headache and are more prevalent in those with more severe forms of headache. Both headache and sleep are strongly influenced by external environmental factors, such as temperature and light, and more internal psychological or cognitive processes, such as thoughts, emotions or moods, or prior experiences [3]. Sleep fragmentation, insomnia, hypersomnia, and circadian rhythm disorders all have relationships with headache. Poor sleep has been found to affect pain perception and trigger the onset and maintenance of next-day migraine in adolescent and adult patients. Sleep disorders, particularly insomnia and obstructive sleep apnea (OSA), increase the risk of transformation from episodic migraine (EM) to chronic migraine (CM). Conversely, sleep is known to relieve headache symptoms [4, 5], and a significant improvement in headache can precipitate from the appropriate handling of sleep disorders [6].

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More specific correlations between headache and sleep have also been described in various primary headache disorders. For example, chronic paroxysmal hemicrania and cluster headache (CH) have strong relationships to rapid eye movement (REM) sleep, and hypnic headache (HH) occurs during non-REM sleep [3, 7]. Sleep-associated headache disorders are generally thought to stem from disrupted sleep. On the other hand, primary headache disorders such as migraine, CH, chronic paroxysmal hemicrania, and HH may, in turn, result in sleep disruption [8].

Anatomy of Sleep and Headache

The anatomy and pathophysiology of headache are quite complex, a result of the associated features which may precede, accompany, or outlast the pain component [9]. The peripheral innervations of the pain-sensing cranial vasculature and dura mater are composed of mainly C-fibers (unmyelinated) or A-fibers (thinly myelinated) nociceptors, which have their cell bodies in the trigeminal ganglion and project to the trigeminal nucleus caudalis (TNC) and associated cervical levels, forming the trigeminocervical complex (TCC). The central process of numerous parasympathetic and sympathetic fibers terminates in the superficial lamina of the dorsal horn (I–V) and synapse on second-order dorsal horn neurons, dividing into three major ascending pathways – trigeminothalamic, trigeminoreticular, and trigeminomesencephalic [10]. There is also a reflex connection from the TCC to the parasympathetic system utilizing the sphenopalatine ganglion resulting in autonomic features of the headache and efferent connections from facial and cervical dermatomes [11–13].

Sleep has an equally complex interplay of anatomical structures with their unique physiological functions. The suprachiasmatic nucleus (SCN), located within the hypothalamus, receives direct and indirect retinal projections and mediates the entrainment of the internal free-running circadian clock to the external light-dark cycles, serving as the circadian control center. A variety of neural systems are involved in wake-promoting processes, such as the cholinergic basal forebrain, cholinergic and aminergic brainstem, and hypothalamic orexinergic pathways. Another hypothalamic system, primarily utilizing orexin and located in the lateral and posterior hypothalamic nuclei, is believed to be wake stabilizing by increasing firing rates in the tuberomammillary nucleus (TMN), locus coeruleus (LC), and dorsal raphe (DR) nuclei [14–18]. Additionally, a cluster of hypothalamic melatonin-concentrating hormone neurons parallels the orexinergic system but, unlike the other systems, is most active during REM sleep and is believed to inhibit the wake-promoting systems [19]. Finally, the sleep-promoting ventrolateral preoptic (VLPO) neurons, which are generally inhibited by the wake-promoting centers, become activated and exert an inhibitory tone on those centers, facilitating the transition from wake to sleep [10].

Anatomical and Pathophysiological Connections Between Headache and Sleep

Thalamus

The thalamus is a pivotal relay center for both pain and sleep. It receives direct ascending projections from the TCC, and the ascending trigeminothalamic projections form a component of a pain neuroaxis, which is vital for nociceptive processing and the integration of sensory, cognitive, and affective responses to pain. These systems are activated during migraine and CH [20–23]. Thalamic neurons also show unique activity patterns during the sleep-wake process [24]. They are depolarized during wakefulness, causing tonic activity of thalamocortical circuits and transmitting sensory information to cortical structures [25]. As one enters into slow-wave sleep, these same neurons switch to a hyperpolarized state resulting in rhythmic burst patterns to limit the sensory stimuli from reaching the cortex, engendering sleep maintenance akin to a form of sensory dissociation. In turn, these burst patterns can be inhibited by the ascending brainstem and basal forebrain wake-promoting circuits, enshrining the thalamus as a pivotal regulating structure in each condition [10].

The thalamus may also play a role in light integration with reticular ganglion cells sending indirect projections via the thalamic nuclei on their final destination to the hypothalamic SCN. The paraventricular thalamic nuclei receive direct input from the SCN and house one of the densest clusters of orexinergic innervations in conjunction with the wake-promoting noradrenergic LC [26–28]. Although this direct photic input is thought to be responsible for entraining the thalamocortical circuits to the light-dark cycle, it is this same input that has been considered to play a pivotal role in photophobia seen in multiple headache syndromes via the involvement of the posterior thalamus [29]. These posterior thalamic neurons, mainly along the dorsal border, have been linked to the individual aversion to and pain-promoting effect of light due to receiving convergent inputs from the dural vasculature and retinal ganglion cells [10].

Hypothalamus

The hypothalamus is involved in coordinating patterned responses, including pain modulation and conducting lower brain center activity in producing a homeostatic response [30]. Headache is often thought of as the culmination of a cascade of altered homeostasis, usually not triggered by extreme conditions but alterations in more basic physiological patterns, such as sleep and stress [31]. The hypothalamus is fundamentally linked with numerous areas of the pain neuroaxis, including the cortex, thalamus, amygdala, periaqueductal grey (PAG), and the dorsal horn of the spinal

cord. Stimulation of these nuclei can induce an antinociceptive effect on spinal cord neurons [32]. The clearest example of the relationship between the hypothalamus and headache is in the trigeminal autonomic cephalalgias (TACs), particularly CH with its characteristic seasonal and circadian rhythms, endocrine dysfunctions (notably melatonin), and associations with sleep [21]. However, there is also evidence that posterior hypothalamic activation, in addition to pontine activation, occurs during a migraine, implying that hypothalamic and brainstem activation may be a feature of all primary headache disorders and craniofacial pain in general [33, 34].

The association between the hypothalamus and sleep is predicated on orexinergic neurons, located in the posterior, lateral, and dorsomedial areas, which likely play a role in circadian modulation [35]. A study by Xie et al. in 2008 demonstrated that hypothalamic orexinergic neurons are involved in the descending inhibition of pain, which happens during stress-induced analgesia [36]. The hypothalamus of persons with CH is abnormal, and stimulation of the posterior hypothalamic nuclei has been utilized as a promising treatment, although a noticeable adverse effect is sleep disturbances [37–39]. Orexinergic neurons are involved in narcolepsy via their selective loss and in alteration of nociceptive activity in the trigeminal nucleus caudalis via activity in the ventrolateral PAG [40, 41]. Narcolepsy is correlated with an increased prevalence of migraine and tension-type headache (TTH), which will be discussed later in this chapter.

The circadian nature of several headache disorders strongly implies the involvement of the SCN as it is ideally placed as an interface between headache disorders and sleep, receiving afferents from the retina, thalamic intergeniculate leaflet, and serotoninergic projections from the midbrain raphe involved in the setting of state-related signals, such as arousal [26, 27, 42–45]. The SCN has efferent connections to a myriad of hypothalamic nuclei, including the VLPO and the lateral hypothalamus, mainly via the orexinergic neurons, and acts via inhibitory GABA-ergic activity [27, 42, 46–49]. These GABA-ergic projections promote sleep by decreasing activity of the monoaminergic structures in the lateral hypothalamus (orexin), LC (norepinephrine), DR (serotonin), and TMN (histamine) as well as conversely decreasing the inhibitory drive to orexin neurons to promote wakefulness, essentially establishing a "sleep-wake switch." Although poorly understood, this sleep-wake switch is thought to be mostly controlled by the thalamus via coalescing thalamic sensory gating, hypothalamic sleep regulation, and pain-modifying structures into more discretely organized functions.

The A11 nucleus is another hypothalamic nucleus that may be involved in the pathophysiology of headaches and sleep mainly via dopamine. When activated, this nucleus directly inhibits activity on the dorsal horn of the spinal cord, which in turn inhibits TCC neuronal firing. Conversely, when the A11 nucleus is inactivated, this leads to pronociceptive signals from a prospective tonic inhibitory drive on the trigeminovascular system [50, 51]. Sleep is also affected by the A11 nucleus, as it is thought to function as an anatomical source of restless leg syndrome [52].

In conclusion, although there is not a clear-cut "headache generator" in the hypothalamus, it is quite plausible that dysfunctional hypothalamic activity gives rise to both altered sleep-wake function and altered pain processing via its orexinergic neurons.

Brainstem

The higher brainstem, as a diencephalic circuit, is a prime location of interaction between pain and sleep systems. Collaterals from neurons in TNC synapse on the nucleus of the solitary tract (NTS) and the parabrachial nucleus (PBN), facilitating contact with all facets of central autonomic control. The NTS is the main nucleus for viscerosensation, playing a role in respiratory, gastrointestinal, and cardiovascular reflex loops. Similarly, the PBN has viscerosensitive functions but is at a more sophisticated level of regulation and communicates more visceral information to the thalamus, hypothalamus, and cortex than the NTS [30]. Together, the TNC, NTS, and PBN form networks that modulate pain, arousal, sleep, sympathetic and parasympathetic efferent activity, and neuroendocrine function. Conversely, nociceptive information can be affected by feedback by these same networks, establishing an ardent link between headaches and sleep [53].

Headache pathophysiology involves the activation of discrete brainstem areas that form part of the pain neuroaxis, including the trigeminovascular system, thalamus, hypothalamus, rostral ventromedial medulla (RVM), nucleus raphe magnus (NRM), and PAG. This network can cause both anti- or pronociceptive effects, which are especially prominent in the RVM, as this can maintain heightened pain states such as allodynia [54]. RVM on-cells are especially active during wakefulness; thus, any boost in their activity may affect sleep, contrasting with off-cells, which are most active during sleep and prevent awakening secondary to nociceptive sensory stimulation. Additionally, there is a REM-off region that is composed of the ventrolateral periaqueductal grey (vlPAG) and the lateral pontine tegmentum (LPT) and receives input from orexinergic neurons. This region exhibits the most substantial activity during wakefulness and is relatively subdued during REM sleep. It is likely this altered function that is responsible for disorganized brainstem modulation in both headaches and sleep disorders [28, 55, 56]. Lesions of this region lead to severely disrupted sleep-wake patterns, while pathological PAG lesions may result in headache [57–61].

The LC is heavily involved in the ascending wake-promoting network, including the ventral PAG, dorsal and median raphe, and TMN. It also stabilizes sleep-wake transitions via receipt of a dense supply of wake-promoting orexinergic fibers [28]. Its activity is greatest during wakefulness but can be intensified during stressful situations [62]. Neuronal activation falls during nREM sleep and is quiet during REM sleep. Norepinephrine is the pivotal excitatory neurotransmitter in ascending wake-promoting networks and is inhibitory at sleep-promoting nuclei such as the ventrolateral and median preoptic hypothalamic nuclei [14, 63–67].

The role of the LC in headache is not as well understood as in sleep, but new discoveries are being made in this endeavor. The LC is the primary site of noradrenaline synthesis in the brain and receives afferents from the paraventricular hypothalamic nuclei and the TCC nociceptive neurons [68, 69]. Stimulation of the LC results in a decrease in intracranial blood flow via α2-adrenoceptors, alongside activation of pontine regions implicated to precede and propagate migraine [20,

70–72]. There is also a frequency-dependent increase in extracranial blood flow, indicating that the LC can cause cerebrovascular blood flow dynamic changes that might contribute to trigeminovascular modulation and migrainous cortical phenomena cortical spreading depression (CSD) [73].

Pharmacology of Headache and Sleep

Adenosine

Adenosine is a compound that plays a pivotal role in a multitude of multiple bodily functions, including energy metabolism, neuronal activity, sleep, and headaches [74]. A byproduct of ATP degradation, adenosine is a local signaling molecule with inhibitory, cytoprotective, and vasodilatory roles, whose activity is coupled to energy metabolism [75]. Adenosine acts as an endogenous somnogen via accumulation in the brain, particularly in the critical sleep-wake transition regions of the basal forebrain and cortex, following energy consumption during wake time [76–78]. Adenosine bolsters sleep and curtails wakefulness by inhibiting the activity of wake-promoting regions via A1 receptors and enhancing the activity of sleep-promoting centers via A2a receptors [79–82]. Caffeine, a potent adenosine A1 and A2a receptor antagonist, is noted to impede sleep and relieve headache while also being a possible precipitating factor in the latter, particularly during withdrawal periods [83–86]. The influence of adenosine on both sleep and headache is predicated on its exact point of action and distinct receptor expression, as evidenced by the influence of adenosine on lateral hypothalamic orexinergic neurons [87, 88].

Adenosine suppresses the wake-promoting activity of orexin neurons via A1 receptors, which are known to modulate the trigeminovascular system at multiple points [89–91] and can inhibit nociceptive afferents in experimental animal models [92] and reduce the nociception-specific blink reflex in humans [93]. Adenosine has been used as an adjunct or replacement for opiate analgesia, with side effects including flushing and headache [94]. There is also an interaction between adenosine and serotonin, which may balance thalamic sensory gating during sleep stages, which signals far-reaching implications on thalamocortical networks [95]. Adenosine plays an additional role in headache disorders via multiple pathways. A genetic polymorphism of the A2a receptor is linked to migraine with aura. Higher levels of adenosine are observed during headaches, and those with higher plasma adenosine levels are more easily able to trigger migraine attacks [96–99].

Melatonin

Melatonin is a hormone derived from serotonin and produced by the pineal gland in a 24-h circadian pattern and closely entrained by the SCN. The secretion of melatonin begins when daylight wanes; peak levels occur at midnight and dwindle later in

the night and early morning hours [100]. High levels of blue light inhibit melatonin secretion, and low levels of blue light promote melatonin secretion. The full range of effects of melatonin are complex and may involve opiate, benzodiazepine, serotonergic, and dopaminergic systems [53].

Melatonin has strong connections to sleep and headache, with one of the strongest associations demonstrated in CH and its well-known circadian and circannual, or seasonal, phenotype. Studies of CH have identified abnormal melatonin secretion patterns, characterized by diminished release and altered expression timing [101–104], namely, as a phase advance during the cluster period. Melatonin alterations have also been observed in independent studies in women with migraine via decreased urinary melatonin and 6-sulphatoxy-melatonin [105–107], particularly in the luteal phase. As menstrual migraine usually occurs between the end of the luteal phase of one cycle and the beginning of the subsequent cycle, this difference could be pertinent. Alterations in melatonin secretion in people with migraine have been shown to increase light sensitivity as compared to controls [105].

Targeted therapy with melatonin in a placebo-controlled trial showed a reduced headache frequency in episodic, but not chronic, CH [108] with a proposed mechanism of altered melatonin homeostasis affecting trigeminovascular nociceptive tone. Melatonin may also halt CSD and the resultant trigeminovascular activation, stressing the significance of its growing target for headache treatment [109]. There have been no placebo-controlled trials of melatonin in migraine, but a myriad of case reports and observational studies reinforce the idea of a possible effect [110].

Orexin

The orexins are neuropeptides that are exclusively produced in the hypothalamus and project to almost the entire CNS [28, 111]. They were first thought to be involved in feeding, but this was later attributed to arousal effects. Orexins are thought to promote wakefulness by stabilizing the sleep-wake transition "flip-flop" switch [56, 112]. They actively support wake-promoting monoaminergic and cholinergic hypothalamic and brainstem neural networks to vitalize wakefulness [15–17, 113]. The disruption of orexinergic signaling results in significant sleep disruptions and sleep disorders, particularly narcolepsy [114]. Orexinergic neurons receive potent projections from limbic structures, inferring a shared point for the combination of emotional stimuli on both arousal and pain [115, 116].

Orexin neurons are regulated by the peripheral hormones ghrelin and leptin as well as glucose, implicating a potential role in energy homeostasis integration, which may help to link a proposed relationship between headaches and diet [117]. Of note, direct hypothalamic administration of orexin-A is antinociceptive, while orexin-B is pronociceptive likely via contrasting actions on the orexin 1 (OX1R) and 2 (OX2R) receptors [118]. Orexin neurons are fundamentally integrated with key brainstem and diencephalic areas activated during headache attacks, with peak activity levels during wakefulness and nascent levels during sleep. In contrast to the clear genetic association between orexin and narcolepsy [41, 114, 119–121],

the association between orexin and headache is equivocal. Several studies have reported positive findings for OX1R and OX2R [122–125], including a two- to fourfold higher prevalence of migraine in people with narcolepsy [126], while other studies have challenged this association [127]. The observation that people with narcolepsy experience the onset of migraine about 12.5 years after the diagnosis of narcolepsy may indicate a causative role of orexinergic disturbance via destabilization of hypothalamic networks [126]. Further investigation into the orexinergic system is warranted, particularly given its significant regulatory role in nociceptive processing and the successful insomnia treatment with dual orexin receptor antagonists, which also show promise in the trigeminovascular system [128].

Nitric Oxide

Nitric oxide (NO) is a ubiquitous signaling molecule that plays a role in many biological processes, including endothelial-dependent vasodilation [129]. NO synthases (NOS) are a group of enzymes that accelerate NO production, with one of the main sites of action being neuronal tissue. Neuronal NOS is found within REM modulating structures, such as the PPT, LDT, and dorsal raphe nuclei, and its disruption logically results in decreased REM sleep [130–133]. NO donors, such as glyceryl trinitrate, can precipitate headaches and associated prodromal symptoms [129, 134–137]. Nonspecific blockade of NOS thwarts neurogenic dural vasodilation and TCC neuronal activation and has shown some clinical efficacy in headache treatment [138–141]. Given the dynamic role of NO donors in provoking headaches and their continued prominence as a pharmacological target, their involvement in the relationship between sleep and headaches should become more distinct over time.

Specific Headache Disorders and Sleep

Headache and sleep have a strong bidirectional relationship, as subjects with chronic headaches are 17 times more likely to have severe sleep disturbances than headache-free individuals [142]. This association is most commonly seen in migraine and will be expanded upon later in this chapter. However, there are other headache disorders particular to sleep, categorized as (1) sleep disturbances as the cause of the headache (i.e., morning headache as a symptom of sleep apnea), (2) headache as the cause of the sleep disturbance (i.e., sleep disruption induced by CH), and (3) a possible overlap of headache and sleep disorders or sharing a common cause (i.e., CM and insomnia induced by mood disorders) [143]. It is well established that patients with insomnia and CM are at a higher risk for mood and anxiety disorders [5].

Primary headache disorders regularly occur during sleep, speculating an association with the pathophysiology of sleep itself [144]. Likewise, disturbance or dysregulation of sleep is a well-known acute headache trigger. The International Classification of Sleep Disorders 3rd edition (ICSD-3) defines sleep-related headaches as headaches that occur during sleep or upon awakening from sleep [145]. These headaches share the common feature of presenting during or following sleep in addition to the daytime (e.g., migraine, CH) and solely during sleep (HH) or arise from other unspecified medical, neurological, psychiatric, or sleep disorders. Differential diagnoses include febrile illnesses, acute infections such as ear, dental, or sinusitis, benign idiopathic intracranial hypertension, sleep-related bruxism, or substance use.

Cluster Headache

There is compelling evidence that supports a relationship between CH, sleep, and circadian rhythms and points toward a pivotal role of the hypothalamus, as discussed previously [21]. There have also been documented changes in the secretion of several important circadian rhythm hormones in people with CH, particularly melatonin, cortisol, growth hormone, thyrotropin, prolactin, and testosterone [146]. The information above may offer some clarity as to why CH attacks usually occur at the same time each day and with specific peak times.

The concordance between CH and sleep has long been described with its typical critical onset during nocturnal sleep. Most attacks commence about 90 min after sleep onset, which is a time period that generally syncs with the beginning of the first REM sleep phase in a typical adult [147]. In contrast, a study by Pfaffenrath et al. in 1986 found that there was an association between CH attacks and REM sleep only in people with chronic CH and not explicitly in episodic CH [148]. A later study by Barloese et al. in 2015 demonstrated that the relationship between CH and REM sleep is not related to REM sleep itself, as attacks can happen in any sleep stage, but may be funneled through hypothalamic dysregulation with hypoarousal during sleep, which is seen in other headache disorders including HH and migraine [149–152].

The sleep disorder most intertwined with the critical period of CH attacks is transient insomnia, which tends to dissipate when the cluster cycle itself finishes [153]. In addition, there is likely a relationship between CH and nocturnal sleep-disordered breathing (SDB) due to the nighttime attack onset and response to oxygen during the acute attack phase. However, Barloese et al. assert that sleep apnea and CH exist in parallel and not in tandem. The clinical implication here is that CH alone is not a signal for further sleep investigation to assess for sleep apnea [149]. Although it is unlikely that SDB causes CH, it can worsen the attacks. Other large-scale population studies and prolonged observational periods are needed to explore this connection [154].

Hypnic Headache

HH is a rare headache syndrome, characterized by recurrent attacks occurring exclusively during sleep (either nighttime sleep or daytime nap) in people older than 60 [155]. HH may be the better model (as opposed to CH) of the correlation between headache and sleep as attacks generally happen with impressive consistency at the same time every night. The moderate to severe pain lasts from 15 min to 4 h and can recur up to four times a night. Raskin, who first described the disorder in 1988, closely correlated the attacks to the REM sleep phase, possibly due to hypothalamic dysregulation. This theory has since been supported through polysomnographic studies [156]. The strong correlation between HH and REM sleep may also be related to a nocturnal oxygen saturation decrease, but there is currently no definitive study to prove this link. Lastly, HH may also be associated with sleep physiology, given its emergence in older people who are undergoing a multitude of sleep architecture changes during the aging process [8].

Tension-Type Headache

Tension-type headache (TTH) is often associated with sleep disturbances such as hypersomnia, insomnia, and circadian rhythm disturbances. The Third Nord-Trondelag Health Study, a Norwegian population study, found that subjects with TTH were three times more likely to experience severe sleep disturbances than headache-free individuals [142]. Those with TTH have a lower total amount of global nocturnal sleep, reduced sleep efficiency and quality of rest periods, shorter sleep latency, and earlier and more frequent awakenings with a reduction of slow-wave sleep but unchanged REM periods. Sleep profiles in people with TTH are very similar to those seen in sufferers of depression and related mood disturbances, fibromyalgia, musculoskeletal disorders, and pain [157]. Studies have demonstrated that both lack of sleep and excessive sleep can trigger TTH [158] and that sleep disturbances are associated with an increased risk of chronic TTH (CTTH) among those with frequent episodic TTH (ETTH) [159]. Additionally, among persons with TTH, those with insomnia experience more frequent headaches, increased rates of psychiatric disorders, and more severe disability due to headache [160].

Migraine

The interplay between sleep and migraine is unequivocal. There are many sleep disorders that can contribute to disrupted sleep in migraine and occur more frequently in migraineurs compared to controls. These include insomnia, snoring and SDB (especially OSA), movement disorders, circadian rhythm disorders, and

parasomnias. Sleep transitions and patterns may play a role in the onset of migraine, as attacks can occur after short periods of daytime sleep, during nocturnal sleep, and upon awakening [161]. REM sleep is the sleep stage generally implicated in migraine attacks, while morning arousal headaches are associated with both slow-wave and REM sleep. Polysomnography (PSG) studies in people with migraine have demonstrated a temporal relation between headaches and sleep onset and REM sleep [157]. Conversely, sleep has led to the termination of a migraine attack, especially in the pediatric population [162].

People with short sleep syndrome, who consistently sleep for less than 6 h each night without an increased need for naps or "make up" sleep and without compromised daytime functioning, have a greater tendency to migraine attacks during nocturnal sleep and are also more likely to awaken with a headache [53]. In the Norwegian Third Nord-Trondelag Health Study, migraineurs were three times more likely to experience excessive daytime sleepiness and five times more likely to report severe sleep disturbances compared with headache-free individuals [142]. In further support of these findings, a case-control study by Barbanti et al. in 2007 reported an increase in reported excessive daytime sleepiness in people with migraine as compared to controls [163].

Temporal patterns are common in people with migraine as 60% of this population report a specific sequence to their attacks [164]. A study by Van Oosterhout et al. showed that, among those identifying a diurnal pattern of headaches, 35% noted attacks predominantly emerging during standard sleep times (midnight to 6:00 AM), and 32% noted attacks mainly occurring during typical morning waking hours (6:00 AM to noon) [164]. Migraineurs were more likely than controls (49% vs. 39%) to have an early chronotype, an endogenous internal circadian rhythm described as a "morning lark" or earlier morning persons. Persons with migraine were also more adversely affected by sleep loss and schedule changes than controls, especially with the chronic form of migraine. A study by Sullivan and Martin in 2017 of 378 Australian participants found that poor sleep quality was the strongest correlate of both migraine and other headaches, which was also found to mediate the effect of sensitivity to headaches precipitated by lack of sleep. Morning chronotype as a significant predictor of CM was confirmed. In contrast, evening chronotype, or those with an endogenous internal circadian rhythm described as a "night owl" or late-night persons, and anxiety significantly predicted a chronic non-migraine headache diagnosis. This finding stresses the need for further investigations into the role of chronotype in headache etiology [165].

Multiple studies have shown that sleep dysregulation (i.e., sleep deprivation, oversleeping, disturbed sleep) is a common precipitant of migraine attacks. In a meta-analysis of 85 headache trigger publications, 40 unique headache triggers were identified, the most common being sleep and stress [166]. In a study by Houle et al., which observed the effects of sleep duration and stress on headache severity in people with migraine and TTH over 28 days, headache was less likely following sleep periods of 7–8 h. Also, headache intensity increased at either end of the sleep duration curve, whether that be short sleep (<6 h) or long sleep (>8.5 h) periods [167]. Further analysis that examined the correlation between headache, sleep, and

stress over 3-day periods concluded that headache was best predicted by a model combining sleep and stress variables with sleep being the driving factor in moderating the stress/headache interplay [168]. Headache severity was worst under a combination of high stress and a short sleep period, while low stress and adequate sleep were protective against headache. This information further supports the role that sufficient sleep may act as a buffer against stress, confirming the importance of sleep regulation as part of an effective treatment regimen for headaches.

Sleep Apnea Headache

Sleep apnea headache (SAH) is classified as a metabolic headache that is attributed to hypoxia or hypercapnia. The exact criteria from the International Classification of Headache Disorders 3rd edition (ICHD-3) stipulate that (1) the patient was diagnosed with sleep apnea (Apnea/Hypopnea Index (AHI) $\geq$ 5/h of sleep); (2) headache is either chronic (15 $\geq$ days/month), has bilateral tension-type features, or resolves within 4 h of waking; (3) the headache onset, exacerbation, and/or resolution is proximally related to sleep apnea related to sleep; and (4) the headache is not better represented by another headache diagnosis [155]. SAH can arise de novo or exacerbate a pre-existing headache condition, and hypoxemia and hypercapnia do not wholly account for its pathogenesis and presentation.

A study by Suzuki et al. in 2015 sampled 235 patients with OSA and found that 20% reported awakening headaches. The diagnoses for the awakening headaches covered a broad range, including tension-type (40%), migraine (25%), cluster (2%), or unclassified (33%) [169]. Of the 48 patients with SAH, 42% had a pressing and bilateral headache without migrainous features such as nausea, vomiting, photophobia, or phonophobia, and 25% had headache frequency consistent with chronic daily headache ($\geq$15 headache days/month).

Specific Sleep Disorders and Headache

Insomnia

Insomnia is the most common sleep disorder in the general population. It is strongly associated with migraine, especially CM, and is a common symptom of anxiety and depression. Emerging research suggests that treating insomnia may improve migraine, further strengthening the bidirectional relationship between them [170–173]. The symptoms, risk factors, diagnosis, phenotypes, and subtypes of insomnia are expanded upon in Tables 6.1 and 6.2. Across all subtypes, however, insomnia is characterized by increased cognitive, somatic, and emotional arousal with a diminished ability to sleep.

A longitudinal study by Boardman and colleagues discovered that insomnia preceded and predicted new-onset headache and migraine exacerbation [174, 175]. In addition, the Nord-Trondelag Health Study, which is a series of population health studies that assessed headache and other variables from over 120,000 people at regular intervals from 1984 to present, found insomnia predicted new-onset headache at 11-year follow-up. The reverse relationship, with migraine as a precursor to insomnia, was also found [176, 177]. Awakening headache, often thought to be a headache pattern more commonly seen in those with snoring and SDB, is more common in patients with insomnia than those with apnea. Chen et al., in 2011, surveyed 268 symptomatic snorers who underwent polysomnography. Morning headache was more common in OSA (27%) as compared to primary snorers (16%), but the adjusted odds ratio (AOR), with adjustments made for age, gender, BMI, and smoking status, for OSA (AOR = 2.6) was less predictive than insomnia (AOR = 4.2), presence of migraine (AOR = 6.5), or psychological distress (AOR = 3.9) [178].

Insomnia is more prevalent in people with migraine, particularly in those with chronic, severe, nocturnal, and/or awakening headache patterns. It is also strongly associated with TTH and other nonspecific headache disorders [179]. In five cross-sectional studies of migraine, the odds ratio for insomnia ranged from 1.4 to 2.6. For three additional studies of nonspecific headache, associations were made for insomnia with severe headache (OR = 2.3), chronic morning headache (OR = 2.1), and

Table 6.1 Characteristics of insomnia [5]

Symptoms
Nighttime symptoms
Difficulty falling asleep (sleep latency >30 min)
Difficulty maintaining sleep (nighttime awakenings >30 min)
Early morning awakenings (earlier than desired wake up)
Non-restorative sleep despite adequate opportunity and environment
Daytime symptoms
Fatigue or malaise
Daytime sleepiness
Impaired attention, concentration, memory; proneness for errors/accidents
Irritable mood, behavioral problems; reduced motivation/energy
Impaired family, social, occupational, or academic performance
Somatic complaints (headache, muscle tension)
Concerns about or dissatisfaction with sleep
Risk factors
Female gender
Increasing age
Mood disorder, anxiety
Past history of insomnia
Family history
Chronic illness, especially pain
Comorbid sleep disorder
Substance use (including caffeine)
Use of medications that impact sleep (stimulants, antidepressants, etc.)

Table 6.2 Insomnia phenotypes and clinical subtypes [5]

Phenotypes
Sleep onset insomnia (sleep onset delayed, norm ≤30 min)
Sleep maintenance insomnia (repeated/extended mid-cycle awakenings >30 min)
Terminal (or late) insomnia (early morning awakenings, before desired rise time)
Combined/mixed insomnia (difficulty initiating and maintaining sleep)
Clinical subtypes
Psychophysiological insomnia (conditioned insomnia, cognitive hyperarousal)
Idiopathic insomnia (often since childhood and unremitting)
Behavioral insomnia of childhood (likely due to improper sleep training or limit-setting)
Paradoxical insomnia (subjectively poor sleep that doesn't correlate with objective sleep measures)
Inadequate sleep hygiene (lifestyle and sleep habits not conducive to sleep)
Insomnia due to mental disorder (anxiety, depression, personality)
Insomnia due to medical condition (i.e., pain, gastroesophageal reflux)
Insomnia due to drug or substance abuse

nocturnal awakening headache (OR = 2.2). Additionally, a study by Sancisi et al. in 2010 showed that low educational levels, lower mean age at headache onset, and insomnia were independently associated with headache. Insomnia may thus be an independent risk factor for headache chronification, and recognition of sleep disorders, either alone or in conjunction with depression or anxiety, may be useful in episodic patterns to prevent chronification [180].

Cognitive Behavioral Therapy for Insomnia

It is crucial to understand how insomnia develops and persists to best embrace its treatment. A diathesis-stress model for insomnia called the "Three P's" is a widely accepted model for the development of chronic insomnia (see Table 6.3) [181]. Individuals all have a varying degree of predisposition for insomnia, stemming from age, gender, personality, and other factors. Precipitants, such as stressful life events, medication changes, shift work, or illness, may trigger acute insomnia in an individual by interacting with their predisposing factors. The majority of the time, acute insomnia resolves as the precipitating event concludes. However, some people continue to have chronic insomnia despite the resolution of the stressor. In these people, perpetuating factors such as maladaptive habits, worry and anticipation of poor sleep, fear of catastrophic consequences of sleep loss, and spending excessive amounts of time in bed to try to sleep are the main driving forces in maintaining insomnia. This worry, fear, and preoccupation regarding the inability to sleep often becomes a self-fulfilling prophecy resulting in a state of "conditioned" or "learned" insomnia as the bed and bedroom become associated with heightened negative arousal. It is these perpetuating behaviors, as well as the cognitive and emotional arousal surrounding them, that serve as the targets for behavioral treatments for insomnia.

Table 6.3 The 3 P's in the development of acute and chronic insomnia [5]

Predisposing factors	Precipitating factors	Perpetuating factors
Biological traits	Stress	Maladaptive habits
Gender	Medications	Excessive time in bed
Age	Shiftwork	Daytime napping
Psychological traits	Medical illness	Irregular sleep schedule
Anxiety-prone personality	Psychiatric illness	Dysfunctional cognitions
Decreased innate homeostatic sleep drive		Worry over loss of sleep
		Feared consequences over lack of sleep
		Unrealistic expectations
		Emotional, physiological arousal

Cognitive Behavioral Therapy for Insomnia (CBT-I) is a widely recommended treatment for insomnia stemming from its safety and long-term efficacy [182, 183]. CBT-I utilizes behavioral interventions to negate learned insomnia, restructure thought patterns that lead to distress and worry about sleep, acquire relaxation skills, and follow sleep habits conducive to sleep. CBT-I differs from CBT used for headache, as stimulus control and sleep restriction are not labor-intensive and can be conducted by trained medical staff in addition to experienced psychologists [184].

CBT-I overall has very few side effects. However, by its very nature, sleep restriction temporarily increases daytime sleepiness, as limiting time in bed is a vital tool in intensifying homeostatic sleep drive, which is pivotal to reach the results of increasing nocturnal sleep and improving insomnia. Patients need to be counseled about a temporary increase in daytime sleepiness. They should exercise caution during activities that could result in higher morbidity due to excessive sleepiness, such as driving or other hazardous activities. Over several weeks, sleepiness decreases as time in bed increases incrementally, and the individual's maximum efficient sleep time is achieved. Sleep restriction should be avoided in conditions exacerbated by a lack of sufficient sleep, such as epilepsy or bipolar disorder. In these cases, a more gradual version of sleep restriction, such as sleep compression, should be utilized.

An abbreviated version of CBT-I that has shown efficacy in the primary care setting can be employed in the appropriate clinical scenario [185]. This intervention uses simplified versions of stimulus control, sleep restriction, and sleep hygiene over two sessions. First, patients are instructed to eliminate sleep-incompatible activities from the bed and bedroom (watching television, using the computer, playing video games, and cognitive exercises that can lead to CNS hyperarousal such as planning or worrying). Second, patients are told to eliminate all daytime naps. Third, patients follow a set bed and rise schedule based on results from a recent 2-week sleep diary. The provider then prescribes the amount of time in bed each patient is allotted, with the time in bed (TIB) determined as the average of that patient's net sleep time per night plus 30 min as calculated from the sleep diary. See the Sleep Restriction Guide (Fig. 6.1) for the exact steps needed to complete this therapeutic exercise successfully.

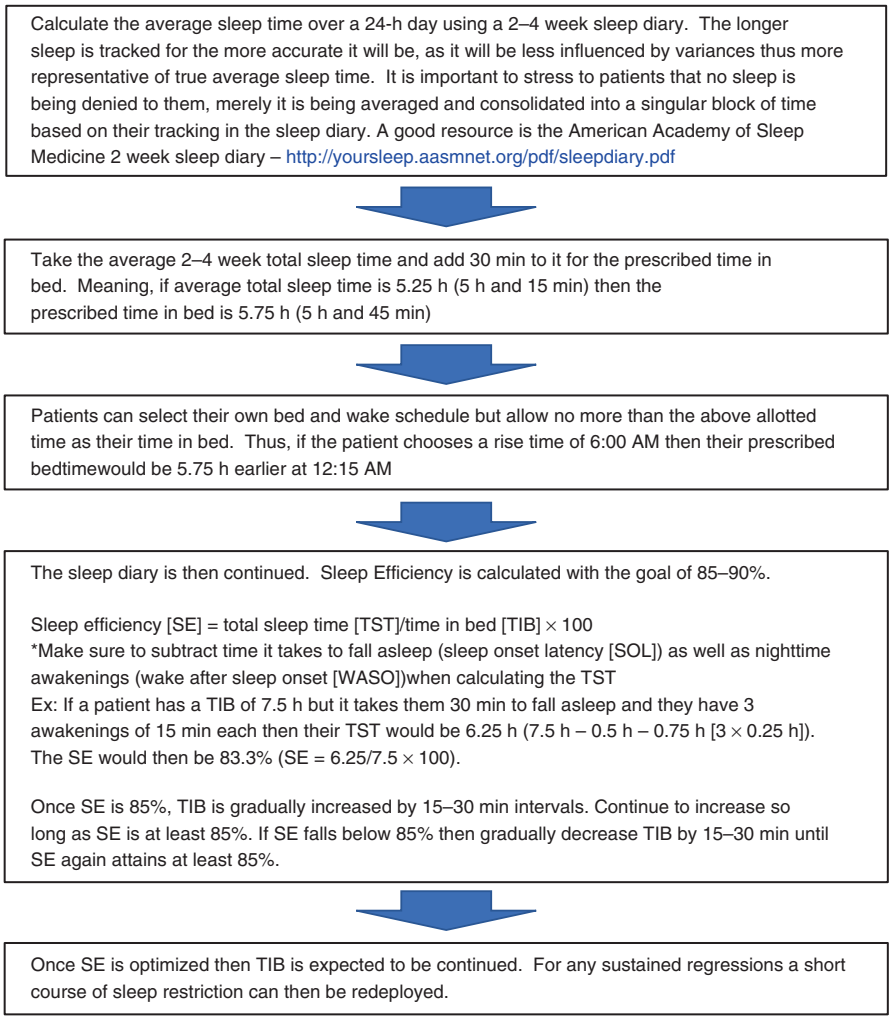

Fig. 6.1 Sleep restriction guide

Patients with CM likely benefit from behavioral sleep interventions, such as CBT-I described above, as treating the sleep comorbidity has been shown to improve headache (see Table 6.4 for specific treatment strategies). Controlled trials by Smitherman et al. and Calhoun and Ford demonstrated improvements in the frequency of CM after a course of behavioral sleep treatment [186, 187]. The results were particularly convincing because each independently demonstrated improvement in migraine frequency utilizing an intervention that solely targeted sleep. Smitherman and colleagues observed that headache frequency was reduced by 6.2 headache days/month in the behavioral sleep treatment group compared to the sham control group at 6–8-week follow-up [188].

Table 6.4 Components of cognitive behavioral therapy for insomnia [5]

Component	Indication	Intended effect	Instructions
Sleep restriction	Excessive time spent in bed not sleeping Frequent awakenings	Increase sleep drive Stabilize circadian rhythm	1. Use sleep diary to determine "time in bed" and "actual sleep time" 2. Restrict time in bed to average number of hours of "actual sleep time" (not <5 h) 3. Prescribe set sleep and wake times. Wake up at set time regardless of how many hours slept 4. Once diary shows sleep time is ≥85% of time in bed, increase by 15–30 min increments 5. If sleeping <85% of time in bed after 10 days, restrict sleep time by 15–30 min increments
Stimulus control	Difficulty falling or staying asleep	Reduce arousal in sleep environment Promote association of bed and sleep	1. Attempt to sleep only when sleepy 2. If unable to fall asleep after 20 min (without watching clock), leave bedroom and try again when sleepy. Repeat as many times as necessary throughout night 3. Use bed for only sleep and sex 4. Set alarm and rise at regular time daily; do not snooze 5. Do not nap during day
Sleep hygiene	Any of the above or poor sleep habits	Reduce behaviors that interfere with sleep drive or increase arousal	1. Limit caffeine and alcohol 2. Keep bedroom dark and quiet 3. Use bed for only sleep and sex 4. Avoid napping 5. Maintain regular bed/wake schedule 7 days/week 6. Increase exercise (avoid within 5 h of bedtime)
Cognitive therapy	Racing, obsessive thoughts at bedtime Catastrophizing or ruminative worry about sleep Unrealistic expectations	Restructure maladaptive beliefs about sleep and sleep loss which provoke anxiety and perpetuate insomnia	1. Identify anxiety-provoking thoughts 2. Apply taught cognitive techniques to challenge perceived catastrophic consequences 3. Set reasonable expectations about sleep
Relaxation therapy	High physiologic, cognitive, or emotional arousal	Acquire skills to gain voluntary control and reduce the state of hypervigilance that is incompatible with sleep	1. Progressive muscle relaxation to reduce physical tension 2. Breathing exercises 3. Meditation

It is unclear if pharmacological management of insomnia would benefit headache. The sole placebo-controlled trial of hypnotic medication versus placebo for migraine by Spierings et al. employed a 6-week controlled trial of the hypnotic eszopiclone 3 mg. The group taking eszopiclone did not exhibit any change in CM frequency as compared to the placebo. The treatment group experienced a decrease in nighttime awakenings, but all headache endpoints were equivalent to placebo, including headache frequency, severity, and duration [189].

Sleep-Disordered Breathing

SDB is an umbrella term for a constellation of sleep-related breathing disorders and abnormalities of respiration during sleep. OSA is the most common SDB disorder although there are close to 20 diagnoses defined by respiratory abnormalities during sleep [145]. The spectrum of SDB ranges from asymptomatic snoring to respiratory event-related arousal to severe OSA with hypoxemia. Mnemonics and validated questionnaires identify high-risk cases that necessitate objective diagnostic testing, which can appropriately pinpoint SDB disorders to initiate timely treatment.

Snoring

The most commonly identified SDB disorder in headache research is snoring, which can only be established as an isolated diagnosis in the absence of apneic pauses in breathing, sleep disturbance, or daytime sleepiness. Snoring can be an accurate marker for OSA and potential SAH, but many snorers do not have the full symptom constellation of OSA. Snoring as a sole disorder does not warrant diagnostic testing; however, this is confounded by the fact that snoring is also the cardinal symptom of OSA. Patients who snore vary significantly on the SDB disease spectrum and their associated morbidities. Primary snoring, even by itself, is not benign, especially when it is loud and irregular [190]. In the absence of OSA, primary snoring is associated with increased cardiovascular risk, thickening of the carotid arteries, and all-cause mortality [190–193].

Obstructive Sleep Apnea

Obstructive sleep apnea (OSA) is defined by AHI $\geq$ 5/h sleep with at least one symptom or comorbidity such as (1) sleepiness, fatigue, nonrestorative sleep, or insomnia, (2) waking from sleep with a gasping or choking sensation, (3) habitual snoring or witnessed apnea by observers, and/or (4) hypertension, mood disorder, cognitive dysfunction, coronary artery disease, stroke, congestive heart failure, atrial fibrillation, or type 2 diabetes mellitus OR AHI $\geq$ 15/h sleep irrespective of

additional symptoms or comorbidities [145]. OSA also infers a wide gamut of additional symptoms such as varying degrees of hypoxia, daytime sequelae, CNS activation with resuscitative arousals, and other comorbidities. For full signs and symptoms, risk factors, diagnostic procedures, and treatments of OSA, please refer to Table 6.5. OSA is also correlated with all-cause mortality, emphasizing the importance of early diagnosis and intervention [194]. Thankfully, tools to evaluate and treat OSA are becoming more widespread, accurate, and cost-effective.

Respiratory Event-Related Arousals

A newer addition to most standard PSG montages, respiratory event-related arousals (RERAs) are sleep-related breathing disturbances characterized by an obstructive upper airway flow reduction (which does not meet criteria for apnea or hypopnea) associated with an increased respiratory effort that resolves with the appearance of arousals. They are preferably recorded with esophageal manometry, but in lieu of

Table 6.5 Characteristics, diagnosis, and treatment of obstructive sleep apnea [5]

Symptoms
Habitual snoring
Witnessed apnea
Waking gasping or choking
Wake up headache
Hypersomnia (or insomnia)
Night sweats
Nocturia
Risk factors
Overweight to obese (especially BMI $\geq$ 35)
Neck circumference (male >17″ and female >16″)
Age (positive correlation)
Family history (especially multiple family members)
Craniofacial morphology (retro or micrognathia)
Oral anatomy (large tongue, uvula, tonsils, Mallampati >3)
Neuromuscular disorders
Substance use (tobacco, alcohol, sedatives, opiates, muscle relaxants)
Diagnostic procedures
Polysomnography (in-lab overnight EEG, EMG, cardiorespiratory, video monitoring)
Portable cardiorespiratory monitoring home sleep apnea test (HSAT)
Treatment options
Positive airway pressure (continuous or CPAP, bilevel PAP)
Oral appliances (mandibular advancement device, tongue-retaining device)
Upper airway surgery
Hypoglossal nerve stimulation
Bariatric surgery for weight loss
Nocturnal oxygen (consider on case-by-case basis)
Conservative options (positional therapy, smoking cessation, non-surgical weight loss, avoidance of substances that increase risk)

this, nasal manometry or induction plethysmography can also be used. The official diagnostic criteria according to the American Academy of Sleep Medicine are (1) a series of respiratory cycles of increasing/decreasing effort or flattening recorded by nasal manometry and leading to an arousal that cannot be defined as apnea or hypopnea and (2) duration ≥10 s [195]. The main utility in identifying RERAs is that it can discriminate pathologic snoring (associated with apneas [cessation of airflow ≥10 s] and hypopneas [>30% decrease in airflow ≥10 s and with ≥4% oxygen desaturation]) from asymptomatic snoring. Previously, if no apneas or hypopneas were found, then snoring was considered "benign." This did not account for those with other respiratory-related sleep disturbances, such as RERAs, which could lead to deleterious effects such as daytime sleepiness, fatigue, and increased risk of hypertension. RERAs are not a formal part of the SAH criteria, but they likely are implicated as an etiology for headaches in some people who snore but do not currently fulfill SAH criteria. Clinicians should be more attuned to the presence of RERAs as a significant source of sleep disturbance, as these could help explain the negative implications snoring may have on sleep in those patients who do not have the typical body habitus or other risk factors stereotypically associated with OSA.

SDB Screening and OSA Diagnosis

SDB disorders can significantly impair daytime functioning and can contribute to the emergence or worsening of other associated medical problems, such as headache. Thus, identification and treatment of these nocturnal respiratory disturbances is of tantamount importance. The Epworth Sleepiness Scale (ESS) and Fatigue Severity Scale (FSS) are two common tools (discussed in more detail later in this chapter) used to help quantify and qualify degrees of sleepiness and fatigue. A limitation of these scales is that they do not differentiate between SDB and other sleep disorders.

The STOP-BANG questionnaire has been developed to more appropriately risk-stratify patients for the presence of OSA, and it has been validated in medical and surgical populations. It is highly sensitive for identifying moderate to severe OSA and follows the mnemonic *S*noring, *T*iredness/sleepiness, *O*bserved apnea, blood *P*ressure 140/90 ≥ mmHg, *B*ody mass index > 35 kg/m^2, *A*ge > 50 years, *N*eck circumference > 40 cm (~15.75 inches), and male *G*ender; three or more affirmative answers denote high risk [196]. The Berlin Sleep Questionnaire (BSQ) has been widely used in research and also helps to risk-stratify patients for possible OSA [197]. It assigns high or low risk based on a patient's neck circumference, habitual snoring or witnessed apnea, and presence of hypertension. The BSQ separates high- versus low-risk patients for OSA with a sensitivity of 86%, a specificity of 77%, a positive predictive value of 89%, and a likelihood ratio of 3.79 [198].

A definitive diagnosis of OSA can only be made using a formal PSG. However, as explained above, there can be a wide gamut of impactful SDB disorders that can have a significant impact in persons with headache. Please refer to Fig. 6.2 for a flowchart to visualize the spectrum of SDB disorders, from normal to severe OSA.

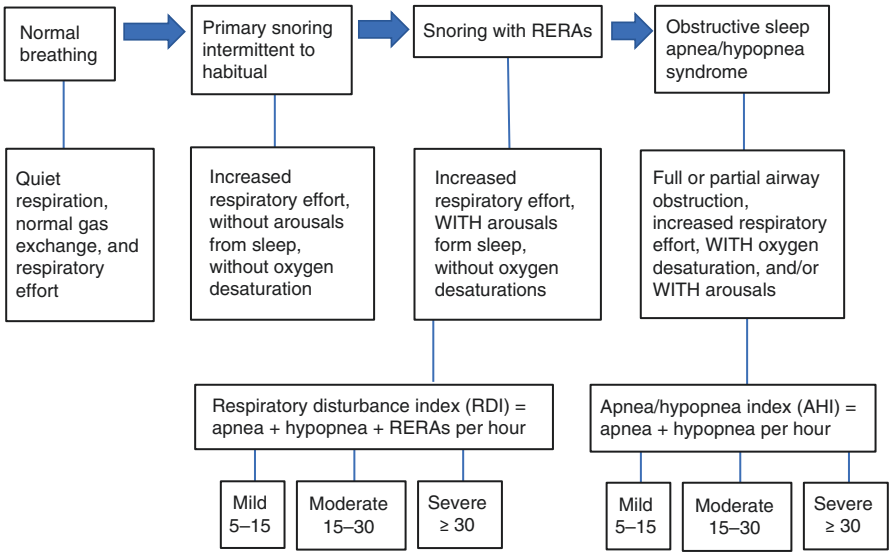

Fig. 6.2 Spectrum of SDB disorders. (Adapted from Rains [5])

SDB Treatments

Numerous treatments for OSA and other SDB disorders are readily available and can be highly effective [199]. In one study, CPAP was the most effective treatment, leading to improvement in >80% of those with SAH [169]. Other studies have found that SAH improved in 33–90% of patients who utilized CPAP as their primary treatment [200–206]. Despite the identification of CPAP as the most widely championed SDB treatment, very little is known about the long-term prognosis of these patients, patients' compliance with CPAP treatment, the exact duration of headache improvement, or the presence of residual headache. It is also unclear if migraine headaches would improve with treatment of snoring and RERAs and the exact point in the disease course that treatment should be initiated for maximal effect. A myriad of non-CPAP treatments also exists, such as oral appliances, upper airway surgery, hypoglossal nerve stimulation, and positional therapy, and these have not been rigorously evaluated in SAH. The bane of CPAP therapy is nonadherence and the leading cause of SDB treatment failure.

SDB, and more specifically, OSA, are chronic conditions, and CPAP is not a curative therapy but merely maintenance. The minimum treatment utilization for CPAP to produce an adequate therapeutic response has been established as at least 4 h of use per night over 70% of nights [207]. A dose-dependent response has been observed with CPAP adherence and its resultant positive outcomes, including reduction of daytime sleepiness and improvement in functional and neurocognitive outcomes [208]. Adherence can be bolstered by behavioral interventions and electronic monitoring, such as the ability for CPAP devices to transmit wireless data and

provide patients with daily feedback scores [209]. Providers can also view this efficacy data and usage patterns and work with patients to enhance facilitation with specific techniques, such as motivational interviewing. CPAP should be continued indefinitely in the absence of other interventions, although recommended and established points for stopping include significant weight loss (usually at least 10% of current body weight) leading to the resolution of OSA or the implementation of other treatments that have either corrected SDB or replaced CPAP. It is assumed that CPAP discontinuation would lead to SAH relapse, although formal studies to examine headache severity and frequency through CPAP withdrawal or to analyze CPAP compliance as a covariant of headache outcome have yet to be conducted.

Restless Leg Syndrome

More recently, restless leg syndrome (RLS), also called Willis-Ekbom disease, has been associated with migraine, indicating there may be a pathogenetic link between the two conditions other than as shared comorbidities [210]. RLS is a common neurological condition and characterized by the International Restless Legs Syndrome Study Group (IRLSSG) as (1) an urge to move the legs usually but not always accompanied by or felt to be caused by uncomfortable and unpleasant sensations in the legs; (2) the urge to move the legs and any accompanying unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting; (3) the urge to move the legs and any accompanying unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues; (4) the urge to move the legs and any accompanying unpleasant sensations during rest or inactivity only occur or are worse in the evening or night than during the day; and (5) the occurrence of the above features are not solely accounted for as symptoms primary to another medical or behavioral condition (e.g., myalgia, venous stasis, leg edema, arthritis, leg cramps, positional discomfort, habitual foot tapping) [211]. Criteria for a diagnosis of RLS in the ICSD-3 are similar to that of the IRLSSG except that distress, associated sleep disturbance, or impairment is required to establish the ICSD-3 diagnosis [145]. The symptoms of RLS cause significant distress or impairment in social, occupational, educational, or other important areas of functioning by their impact on sleep, energy/vitality, daily activities, behavior, cognition, or mood [211].

Idiopathic and symptomatic forms of RLS have been recognized, with the latter occurring during pregnancy or associated with iron depletion, uremia, polyneuropathy, spinal disorders, or inflammatory disorders such as rheumatoid arthritis. The prevalence of RLS ranges from 2% to 15% in the general population, which is likely inaccurate as it is often underrecognized or misdiagnosed [212, 213]. The frequency increases with age, and it is more prevalent in women than men.

An observational study by d'Onofrio et al. in 2008 examined 200 headache patients and 120 sex- and age-matched controls to discern the occurrence of RLS in patients affected by primary headaches [214]. RLS frequency was significantly higher in headache patients (22.4%) than control subjects (8.3%), which was independent of sex, although there was a female preponderance (84%) in both groups. More than 60% of RLS patients were affected by migraine without aura and 30% by a combination of two headache types. Interestingly, no RLS patients had episodic CH. Headache patients with RLS reported sleep disturbances more frequently (50%) than those without RLS (32.7%).

The above study raises the possibility of several pathogenetic links between RLS and primary headaches, with the most intriguing theories involving dopamine and melatonin. The RLS response to dopaminergic therapy suggests a possible role of dopamine in its pathogenesis, and dopaminergic abnormalities have been demonstrated in migraine [215, 216]. An imbalance of melatonin could be involved in RLS and CH, which are both circadian disorders, but with an inverse relationship. A nocturnal increase in melatonin secretion signals the onset and worsening of RLS symptoms resulting in an inhibition of central dopamine secretion. In contrast, a decrease in nocturnal melatonin secretion with lower levels during cluster periods than remissions was demonstrated in CH patients [103, 104, 217]. Another pathogenetic mechanism that could link RLS and primary headaches is the abnormality of brain iron metabolism. Iron is an essential cofactor in dopamine synthesis, and this acts as the bridge between the two primary pathogenetic mechanisms involved in RLS [215]. In persons with migraine, particularly those with CM with a long duration of illness, brain iron storage has been found in the periaqueductal gray matter, which indicates abnormal iron metabolism [218]. Thus, migraine could represent a risk factor for RLS, while CH may be a protective factor. These hypotheses could direct new research into the pathogenesis of and potentially the treatment of migraine associated with RLS.

Sleep Bruxism

Sleep bruxism (SB) is excessive nocturnal teeth grinding or jaw clenching that is unrelated to normal functions such as eating, talking, or breathing. Bruxism itself, whether during awake or sleep, is a common behavior, with a prevalence of 8–31% in the general population, and women are more likely to be affected while awake. Both men and women are equally affected by SB [219, 220]. Complaints of tooth grinding during sleep decline over time, from 14% in children to 12.8% in adults to 3% in people over 60 years of age [219, 221]. Symptoms associated with bruxism include hypersensitive teeth, aching jaw muscles, headaches, tooth wear, and damage to dental restorations (such as crowns and fillings). Symptoms can also be minimal or nonexistent, and thus patients may not be aware that they have bruxism. SB

can lead to disruption of the bed partner's sleep, tooth wear, tooth mobility, tongue/cheek indentation, and masticatory muscle hypertrophy [222, 223]. The symptoms of SB are usually worse on waking and improve during the day. The causes of bruxism are not entirely known but likely involve multiple factors [220].

The diagnostic criteria of SB according to the ICSD-3 are (1) the patient reports or is aware of tooth-grinding sounds or tooth clenching during sleep; (2) one or more of the following is present: [A] abnormal wear of the teeth, [B] jaw muscle discomfort, fatigue, or pain and jaw lock upon awakening, and/or [C] masseter muscle hypertrophy upon voluntary forceful clenching; and (3) the jaw muscle activity is not better explained by another current sleep disorder, medical or neurological disorder, medication use, or substance use disorder [145]. The association between SB and headaches has been discussed in both children [224–227] and adults [228–232]. The pathophysiologies of TTH and migraine are complex and multifactorial, but there is some evidence that dysfunctions of the masticatory and cervical muscles are associated with an increased prevalence of these disorders [233]. It has been hypothesized that SB may cause daytime headaches, and both TTH and migraine have been associated with SB, with an odds ratio indicating a more than threefold risk increase [229, 231, 234].

Pain models for TTH theorize that nociceptive inputs from peripheral tender muscles can lead to central sensitization and CTTH. The possible peripheral mechanisms that result in pericranial tenderness include activation or sensitization of nociceptive nerve endings by the presence of chemical mediators [235]. An updated pain model was proposed by Fernandez-de-las-Penas and colleagues in 2007 in which headache could be somewhat explained by referred pain from trigger points (TrPs) in the posterior cervical, head, and shoulder muscles [235]. TrPs would be the main hyperalgesic zones responsible for the development of central sensitization in CTTH. Bruxism may also be an important contributing factor for the development of TrPs in the head and neck, which subsequently create and/or contribute to TTH and myofascial headache [236]. Supporting this, a study by Glaros and colleagues in 2007 found that patients reported significantly more frequent and intense tooth contact, more masticatory muscle tension, more pain in their head/face, and more stress than controls without headache [237].

Regarding migraine, the most credible hypothesis for the association between SB and migraine is that nociceptive inputs from the masticatory muscles augment the excitability of the trigeminal subnucleus caudalis nociceptive neurons, resulting in an increased risk for migraine attacks. Bruxism-induced muscular changes could also lead to central sensitization of trigeminal subnucleus caudalis nociceptive neurons, which is associated with a higher headache frequency in persons with migraine [238, 239]. Free nerve endings in peripheral tissues provide a significant input for pain. Many of these free nerve endings function as nociceptors, and their activation can result in the production of nerve impulses. The masticatory muscles and the temporomandibular joint contain numerous free nerve endings, and these may respond to a breadth of peripheral stimuli that cause pain [239]. Further research is needed into the treatment of SB and subsequent observation for any headache-related improvement [240].

Circadian Rhythm Disorders

Circadian rhythm disorders are those defined by an alteration in the timing of sleep. These disorders include delayed sleep phase syndrome, advanced sleep phase syndrome, jet lag, and irregular sleep-wave cycles. In delayed sleep phase syndrome, individuals are unable to fall asleep at the desired (normal) time. Their body clock delays their sleep time (e.g., from 10 pm to 4 am), resulting in difficulty awakening at the desired time and daytime sleepiness. Headache can be a symptom of phase disorders, and ingested melatonin can be helpful for both the sleep disorder and the headache itself.

Parasomnias

Parasomnias are distinct abnormal physical phenomena that can occur during entrance into sleep, within sleep, or during arousal from sleep and include sleepwalking or somnambulism, nocturnal enuresis, and night/sleep terrors, among others [172]. Parasomnias are present more frequently in migraineurs compared with controls [241].

Exploding head syndrome (EHS) is a parasomnia characterized by a sudden sense of an explosion in the head that usually occurs during sleep or during the sleep-wake transition [242]. The perceived noises can be quite distressing and cause intense fear and anxiety. However, EHS does not usually cause head pain and is therefore not characterized as a headache disorder. EHS may be more common in women, especially those over age 50, and is an entirely benign condition [242]. The etiology of EHS is unclear and, to date, there are no studies showing a link between EHS and primary headaches. Practitioners should be aware of EHS as it can mimic sleep-related headache disorders.

Evaluation and Treatment of Sleep Disorders in Headache Patients

Despite the knowledge and understanding that headache patients often have comorbid sleep disorders, it can be daunting for the practitioner to tease out the necessary information from these persons and formulate an appropriate treatment plan. With a high number of sleep medicine specialists having longer than anticipated wait times, a practice that at times may be too weighted to those with SDB disorders, and a limited appreciation for the unique challenges that headache patients may pose, often the headache specialist will perceive that the burden of addressing the sleep complaints falls onto them. While these are valid concerns, most patients with sleep complaints may still benefit from a formal evaluation by a trained and licensed sleep

medicine specialist. However, the headache practitioner should act as the initial checkpoint for these patients in the interim, and, with a comprehensive knowledge of the points discussed in detail above, a timely and appropriate initial sleep disorder treatment plan can be devised.

A proposed clinical algorithm for the headache practitioner to approach sleep disorders is provided in this chapter and can be found in Fig. 6.3. It is important to be aware that this algorithm is based on current literature regarding appropriate screening and treatment recommendations for different diagnostic subgroups; however, it is not validated. The main focus is on those persons with CM or chronic tension-type headache (CTTH). However, it may still be worthwhile in those with episodic headaches to minimize the risk of headache progression by focusing on headache trigger management and prophylactic sleep strategies. The specific sequential steps accompanying the treatment algorithm will be explored in more detail below.

Step 1: Determine ICHD-3 Headache Diagnosis

The primary step in effectively addressing sleep complaints and identifying and managing sleep disorders in patients with headaches is to diagnose the exact headache type according to ICHD-3 criteria [155]. A myriad of headache disorders

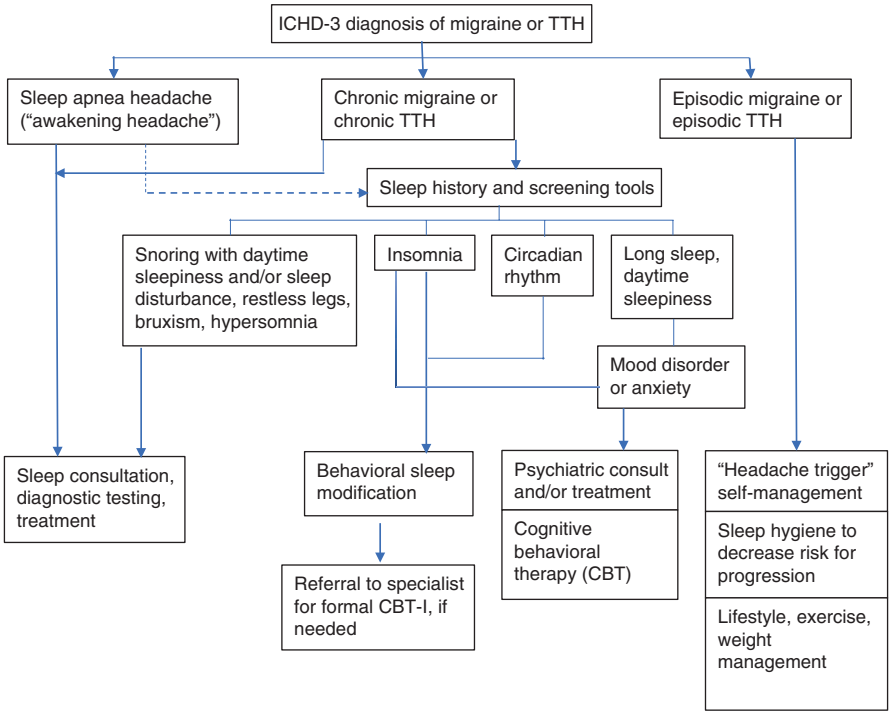

Fig. 6.3 Clinical approach to sleep disorders in headache patients. (Adapted from Rains [5])

exists, but the main focus for sleep interventions is migraine and TTH, specifically the chronic forms. It is prudent for the headache practitioner to familiarize themselves with the ICSD-3, particularly on the diagnoses of insomnia and SDB/OSA. The most recent version of the ICSD-3 has added the diagnosis of "sleep-related headaches" under the umbrella classification of "sleep-related medical and neurological disorders," which indicates a realization of their importance [145]. The most salient components of a headache intake pinpoint pain features and timing, familial patterns, triggers (e.g., sleep, menstruation), progression, effective or failed treatments, behavioral responses to pain (e.g., resting, sleeping, medication), comorbid conditions, and physical exam including orofacial anatomy and body habitus. Specific temporal patterns and sleep-related triggers are more common in patients with migraine, especially CM, but less so for TTH.

Step 2: Collect Sleep History for Awakening Headache in CM or CTTH

Persons with EM and episodic tension-type headache (ETTH) do not have a higher incidence of major sleep disorders when compared to controls. However, an indicator that a more robust sleep history is needed is when the headache, regardless of the frequency, occurs primarily during or following sleep. In persons with CM, there is a high enough risk of sleep disorders to vindicate the collection of a full sleep history, based on diagnosis alone. There is less evidence for this practice in CTTH, but it is likely still prudent.

The sleep history characterizes pre-sleep routines, particularly behaviors that interfere with sleep such as electronics use, consistency of the sleep/wake schedule, latency to sleep onset, nocturnal and early morning awakenings, sleep-disturbing events (e.g., snoring, movements, nightmares, ailments, or pain), awakening headache, daytime sleepiness (e.g., dozing in public or undesirable locations, napping, drowsy driving), and other sequelae (e.g., fatigue, irritability, cognitive impairment, caffeine, other substances). A useful mnemonic that poses pivotal questions to define the quality and quantity of sleep and its impact on daytime functioning is REST. The components to REST are *R*estorative nature of the patient's sleep, *E*xcessive daytime sleepiness, tiredness, or fatigue, the presence of habitual *S*noring, and whether *T*otal sleep time is appropriate. The bed partner can be interviewed, and quantitative measures such as sleepiness or mood scales can also provide a source of supplemental information if needed.

Another important distinction in obtaining an accurate sleep history is the need to discriminate sleepiness from fatigue. The terms sleep, tired, fatigued, drained, exhausted, etc. are used synonymously by people to describe daytime sequela of their sleep or mood complaint. However, fatigue is not equivalent to sleepiness, and sleepiness is more predictive of sleep loss than fatigue. Fatigue is a more subjective experience for which causes include loss of motivation or depressed mood. A scale that can help to quantify the impact that fatigue has on an individual is the FSS with higher scores (especially those >36) indicating a higher level of fatigue. Of note, the FSS has not been formally studied in headache patients [243]. Conversely,

sleepiness can be more objectively measured and compared to normative data. The ESS was validated with PSG and norms available for diagnoses: narcolepsy (17.5 ± 3.5), OSA (11.6 ± 4.6), primary snorers (6.5 ± 3.0), insomnia (2.2 ± 2.0), and normal controls (5.9 ± 3.2). When compared to norms, individuals with primary snoring and insomnia rarely have an ESS score > 10. ESS and FSS help to discriminate sleepiness from fatigue. One point of mention is that the norm ESS score for insomnia is lower than any other diagnostic group and even controls, despite these patients reporting sleepiness. Often these patients feel more a sense of fatigue, despite self-identifying their complaint as sleepiness. Fatigue is also a common premonitory symptom of migraine [244–246]. Persons with migraine had more daytime sleepiness than controls, which has generally been accounted for by poor sleep quality, medications, other mood or medical disorders, and greater headache intensity and disability [247, 248].

Step 3: Identify and Treat Sleep Apnea Headache

It is imperative to rule out OSA in patients with awakening headache or higher-risk headache diagnoses such as CH, HH, CM, and CTTH. Headache patients with signs and symptoms of OSA, usually in the form of SAH (refer to prior SAH section for exact diagnostic criteria) with prominent snoring accompanied by daytime sleepiness or other sleep disturbances, require objective testing. The gold standard for diagnosing OSA and other SDB disorders, narcolepsy, complex cases of insomnia, and injurious parasomnias is PSG. However, full in-lab PSG testing is limited by cost, time, insurance requirements, or other stipulations. Another viable option for formal testing is unattended portable cardiorespiratory monitoring home sleep apnea test (HSAT) or other forms of sleep apnea testing, depending on the details and complexities of the suspected disorders present.

The appropriate circumstances for the utilization of each type of test can be confusing, but with additional examination, there is more clarity. When there is a high pretest suspicion for OSA in the absence of confounding comorbidities, HSAT is adequate for diagnosis and considerably less cost than in-lab testing [249]. Both in-lab and at-home tests produce an AHI or rate of respiratory events. However, home testing usually does not include electroencephalogram (EEG) leads. Thus, while PSG can determine sleep stage via EEG and record AHI per hour of sleep, HSAT records AHI per hour of testing only, as it cannot definitively differentiate between sleep and wake states without EEG leads. Because of this, HSAT tends to underestimate OSA severity as compared to PSG when there are longer durations of periods of wake during testing. Both tests are qualified to identify OSA in moderate to severe cases. However, only PSG can identify RERAs, as the EEG leads are necessary to capture episodes of fragmented sleep with resuscitative arousals but without hypoxemia.

For those persons with migraine who also have SAH, treatment of OSA represents a unique and actionable opportunity for headache to improve or resolve. SAH patients with confirmed OSA necessitate tailored treatment to both their apnea

severity and comorbid disease [145]. Apnea severity is classified by the frequency of respiratory events, consisting of mild (AHI = 5–15 events per hour of sleep), moderate (AHI = 15–30 events per hour of sleep), or severe (AHI ≥ 30 events per hour of sleep). Current best practices recommend that an AHI ≥ 15 warrants treatment with the most efficacious therapy coupled with the most benign side effect profile (such as CPAP). Mild OSA only requires treatment when patients are symptomatic with daytime impairment or have comorbidities such as hypertension and depression [145]. As a result, mild OSA in persons with migraine would only necessitate treatment based on symptoms, comorbidities, and whether the provider believes there is evidence of SAH.

Most treatment studies that resulted in improvement in SAH treated patients with CPAP. Though CPAP is the gold standard therapy for OSA, it is not accepted or tolerated by all patients. Replacements to CPAP include surgery such as uvulopalatopharyngoplasty (UPPP), mandibular advancement devices, tongue-retaining device, Provent© (a nasal therapy which harnesses expiratory positive airway pressure), and positional therapy, among others. The Inspire© hypoglossal nerve stimulator, FDA-approved for the treatment of OSA in 2014, demonstrates promising results in a subset of patients who failed CPAP, have moderate to severe OSA, have BMI ≤ 32, and meet other defined criteria [198].

Step 4: Assess Sleep Disturbance and Insomnia in CM and CTTH

Chronic headache sufferers should be screened for sleep disorders particularly in cases refractory to standard treatments. Insomnia is increased in migraine, especially in those with chronic, nocturnal, and awakening headache patterns. Insomnia is most often diagnosed by sleep history (see Table 6.1) and a sleep diary. A good sleep diary should include (1) bedtime (in bed with lights off with intent to sleep), (2) sleep-onset latency (estimate of time it takes to fall asleep), (3) number and duration of nighttime awakenings, (4) final awakening time, and (5) out of bed time. Diaries can reveal insomnia phenotypes and subtypes including sleep onset vs. sleep maintenance insomnia, early morning awakenings, irregular sleep schedules, and circadian rhythm disorders (see Table 6.2). Once insomnia is diagnosed, CBT-I should be recommended as the first-line treatment.

Step 5: Consider Sleep Regulation in CM and CTTH

Behavioral sleep regulation has been shown to improve CM [186]. The choice of behavioral treatment is based on presenting symptoms and sleep diary information (see Table 6.4). Behavior-based treatments (sleep restriction, stimulus control, relaxation training) are best for patients who spend excessive time in bed not

sleeping, who have irregular sleep schedules, who engage in sleep-incompatible behaviors in bed, or who exhibit evidence of hyperarousal. Cognitive therapy is indicated for patients who have unrealistic expectations about sleep, who fear the consequences of not sleeping, or who have anticipatory anxiety or poor coping skills. All patients should be educated on sleep hygiene, especially those with poor sleep habits, environment, or lifestyle [157].

Step 6: Assess for Psychiatric Comorbidity

Individuals with CM and CTTH are at an increased risk for psychiatric disorders. Insomnia, hypersomnia, and daytime sleepiness are common symptoms of mood and anxiety disorders [5]. Screening for psychiatric comorbidities is warranted in patients who present with these symptoms. In some cases, mood symptoms will improve with the treatment of sleep and migraine. For others, treatment of migraine and psychiatric disorders can exacerbate the comorbid sleep disorder. For example, use of more stimulating antidepressants can worsen insomnia, whereas the use of sedating antidepressants can increase daytime sleepiness.

Step 7: Manage Sleep-Related Triggers in Episodic Migraine

Persons with migraine are often counseled in trigger management. Trigger management is a crucial component in the patient's journey to headache improvement, offering a unique opportunity for them to take agency over the environmental and lifestyle choices that are contributing to their attacks and condition. Improved self-management skills can reduce the reliance on medications and boost feelings of esteem and self-efficacy.

Identification of an individual's triggers, such as stress, sleep, diet, and mood, can be facilitated by the use of a headache diary. Integral components of an effective headache diary include recordings of sleep schedules, quality and duration of sleep, napping, and daytime sleepiness. When identifying a relevant headache trigger, the focus should be on a headache that occurs within 24 h of exposure >50% of the time. Once identified, a trigger can then become a target for self-management or intervention. Auxiliary devices that can further assist in the identification of triggers include electronic diaries and wearable monitoring devices.

Conclusion

There is clear evidence that sleep and headache are related. Nearly all types of primary headaches seem to be frequently associated with poor quality sleep. Likewise, sleep dysregulation is a repeated acute trigger in headache disorders, particularly

migraine and TTH. Research correlating specific headache diagnoses and sleep disorders have shown that the same anatomic structures (mainly the brainstem and diencephalon) are involved in sleep regulation and headache generation. Similarly, sleep mediators, such as orexin, adenosine, and melatonin, likely play a crucial role in many headache disorders related to the sleep cycle, such as CH, HH, and migraine.

OSA is the sleep disorder most often associated with awakening headache. Snoring can be a symptom of or harbinger of OSA and possible SAH. However, many snorers lack the full symptom constellation of OSA. The breadth of SDB disorders ranges from asymptomatic snoring to RERAs to severe OSA with hypoxemia. Further research is necessary to identify the exact threshold for treatment across the SDB spectrum; however, diagnostic testing is crucial when SAH is suspected.

Among patients with migraine and TTH, insomnia is the most common sleep complaint. Patients who suffer from CM and CTTH would likely benefit from behavioral sleep modification. All headache patients, especially those with EM and ETTH, would benefit from inclusion of sleep variables in trigger management. Treating the sleep disorder generally improves the headache, but it is uncertain if pharmacological management of insomnia would positively impact headache. The sole placebo-controlled trial of hypnotic medication versus placebo for migraine demonstrated a lack of improvement in headache frequency, and other headache endpoints were not met although sleep did improve. Additional research down this path is needed.

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Chapter 7
Mind-Body Therapies

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Acupuncture

Introduction

Many patients turn to mind-body therapies for headache because standard pharmacological treatments have many shortcomings, while others incorporate these therapies into their treatment plan as adjuncts. This chapter aims to define commonly used mind-body therapies, to discuss the evidence that supports their use in headache treatment, and to explore how to counsel patients regarding the best way to incorporate these therapies into a comprehensive treatment plan. Within the class of mind-body therapies that will be discussed in this chapter, biofeedback has the highest level of evidence for treatment of headache, followed by acupuncture. There is growing evidence that mindfulness meditation and progressive muscle relaxation are beneficial modalities for headache. Massage, tai chi, and yoga are becoming more widely used therapies for the prevention and treatment of headaches, but their effectiveness remains in question, especially when compared to pharmacological treatments.

In recent years, acupuncture has become a more widely accepted and frequently used form of integrative medicine for the treatment of headache. There are several different types of acupuncture that are commonly practiced. These include body acupuncture, electro-acupuncture, and ear acupuncture. Body acupuncture is the most common type of acupuncture and involves fine steel needles inserted into various acupuncture points on the body. Electro-acupuncture is typically used in conjunction with body acupuncture; the needles are stimulated with an electric current to increase the intensity of the stimulation. Current practices in ear acupuncture

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were established by French physician, Dr. Paul Nogier, in the 1950s. He used the concepts of somatotopic organization and auricular representation to map the different anatomical structures of the human body to the ear [1].

Evidence

Overall, there is growing evidence that acupuncture can be effective for the prevention of both migraine and tension-type headache. The 2016 Cochrane review by Linde is one of the most recent and comprehensive investigations on acupuncture for the prevention of episodic migraine. It concluded that acupuncture is more effective than no prophylactic treatment, more effective than sham acupuncture, and as effective as a pharmaceutical intervention in reducing the frequency of headaches in patients with migraine. The authors found that acupuncture is at least as effective, or possibly more effective than prophylactic drug treatment, and has fewer adverse effects [2]. Linde et al. also published a Cochrane review the same year on acupuncture for the prevention of tension-type headache [3]. Based on data from 12 trials, they concluded that acupuncture is effective in treating frequent episodic or chronic tension-type headaches with a small but significant reduction in headache frequency over six months. However, many studies show that sham acupuncture or simulation acupuncture can be just as effective as true acupuncture, which raises the question: Is acupuncture mostly placebo? There are a few clinical trials that have compared acupuncture to some of our standard migraine preventive medicines such as topiramate and metoprolol and have shown that acupuncture can be as effective as these oral medications for migraine prevention with fewer side effects [4–10]. From a research perspective, there is growing evidence that acupuncture is helpful for migraine and tension-type headache, but more high-quality studies are still needed.

Mechanism

Acupuncture is becoming a more widely accepted form of alternative therapy for the prevention and treatment of headache in the West [11]. Its mechanism of action does not have a clear explanation, but some studies suggest that acupuncture may have anti-inflammatory action via the release of neuropeptides from nerve endings, including CGRP [12, 13]. Other theories suggest that acupuncture may exert analgesic effects by the hypothalamic-pituitary-adrenal axis and the endogenous opioid system, which are essential mediators of the stress response to pain [14].

The first thing patients usually want to know is, how does acupuncture work? What is acupuncture doing to the body? There are two potential ways to understand and explain this to patients. One is through the traditional Chinese medicine point of view in which acupuncture is thought to help regulate and balance the flow of "qi" through the body. In Chinese, "qi" literally means air, but is usually translated as a vital force or energy that flows in the body. The "qi" has an impact on our circulation, nervous system, and all of our vital organs. A helpful analogy is to

envision the body as a New York City subway map. The different colored subway lines are the meridians or energy channels in the body, and the passengers in the subway cars are the "qi" or the energy that is being transported. The goal is to make sure those subway cars are neither too crowded nor too empty and that the whole system runs smoothly. Needling is thought to be a way to add qi where there is a deficiency or to remove qi from where there is congestion. The other way to explain how acupuncture works is through a Western physiology perspective where micro-injury from needling can lead to increased blood flow and healing. Some studies show that acupuncture can lead to change in the levels of certain neurotransmitters such as serotonin and dopamine as well as changes in specific molecules like endorphins, which affect how the body senses pain. The exact mechanism of action of acupuncture is still unknown, and more research is needed.

Patient Selection

The simple answer to who should be getting acupuncture is anyone who is open-minded about it, has discussed it with their medical doctor, and has the time and resources to go through the treatment. Feeling comfortable with acupuncture and believing it is effective are important factors that can affect results. Patients should always check with their doctor about any possible contraindications. Overall, acupuncture is safe and low in side effects if performed by a competent, certified acupuncturist who is using sterile, single-use needles. Some common potential side effects include bruising, bleeding, and soreness [15]. In some people, needling can cause lightheadedness and fainting, which is why acupuncture should be performed with the patient in a prone position. There are three particular groups of people who must consult with a medical doctor before starting acupuncture. The first group is pregnant women. Women who are pregnant should discuss the risks versus benefits of acupuncture with an obstetrician. If the decision is made to proceed with acupuncture, the acupuncturist must be informed of the pregnancy as several acupuncture points can induce labor when stimulated. If these points are stimulated early in pregnancy, miscarriage can result. The second group is patients with bleeding disorders or those who are on blood thinners. These patients may bleed or bruise more than the average person. The third group of patients is those with pacemakers. However, this is only an issue if the acupuncturist decides to perform electro-acupuncture, where electricity is applied to the needle to achieve a stronger stimulation. The electrical pulses can potentially affect the function of the pacemaker.

Treatment Experience

For patients who are undergoing acupuncture for the first time, the treatment process may seem unfamiliar and daunting. It is helpful to counsel patients on what to expect before they arrive at their first session. Patients can eat before their appointment; it is ideal to feel neither hungry nor too full. Patients should wear

comfortable, loose clothing that allows access to the four limbs and the torso. For example, an appropriate outfit could consist of a comfortable T-shirt and loose pants that are easily rolled up to knee level.

The first treatment session typically takes about an hour. The diagnostic methods in traditional Chinese medicine include inspection, listening and smelling, inquiry, and palpation. Before hands-on treatment begins, the acupuncturist takes a medical history. Patients should inform the acupuncturist of all ongoing medical issues. Then the acupuncturist performs a physical exam. Two critical parts of the exam are palpating the pulse and examining the tongue. The pulse and tongue diagnosis help to guide the acupuncturist's treatment plan. Palpation provides diagnostic measurements related to the causes of disease, the location of disease, the nature of disease, and predictions of treatment course [16].

For the needling, the patient will usually be asked to lie down on a padded bed. For warmth, most offices will have heat lamps and warm towels or blankets to keep the patient warm. Then the acupuncturist will choose the points and start inserting needles. Many patients will ask if the needles hurt. Some needles are initially painful when inserted, and some are painless. It depends on the area of the body where the needle is placed. Once the needle goes in, the acupuncturist may thrust or twist the needle until the patient feels a warm or tingling sensation called "deqi." Usually, the average number of needles inserted each session is 5–20. Once the needles are inserted, the acupuncturist will set a timer before leaving the room. The needles remain in place for about 20 to 45 minutes. During that time, the patient should breathe, relax, and nap. There is typically a call button placed beside the patient if the patient needs help or if something needs to be adjusted. Once the timer is up, the needles are removed, and the session is complete. It is important to recognize that, after the session, patients should avoid vigorous exercise, sexual activity, and alcohol and caffeine for the remainder of the day. The goal is to avoid overstimulating the body on the day of treatment, as acupuncture is quite stimulating itself.

Setting Expectations

Patients experience a range of results after undergoing acupuncture treatment. Frequency, duration, and consistency of treatments can have an impact on results. A standard round of acupuncture is typically comprised of one to two sessions a week for a total of eight to ten sessions. Patients need to understand that acupuncture requires a commitment of time and resources.

Patients must also understand that with acupuncture, as with other treatments, there will be super responders who do particularly well, non-responders who do not experience any benefit, and partial responders. The severity and chronicity of disease can be an indicator of how effective the treatment will be and how long and how intense the treatment needs to be. The less severe the disease, the easier it is to treat. For example, if the patient has a history of a few headache days per month with a recent uptick in frequency, then a round of eight to ten sessions of acupuncture may make a significant difference, whereas, for a patient who has had daily headaches for the last 20 years, a few sessions of acupuncture may not impact

symptoms significantly. For patients with chronic migraine who have tried many treatments already, acupuncture can still be a useful supportive or adjunctive treatment. Acupuncture can help with co-morbid issues such as poor sleep, anxiety, and muscle tightness. These issues can have a substantial impact on migraine, and treatment can help reduce migraine burden. If patients are open to addressing co-morbid issues, then acupuncture may be reasonable to try.

Massage

Introduction

Massage is defined as the conscious manipulation of soft tissue (muscle, fat, connective tissue, and skin) for therapeutic purposes [17]. It is one of many manual therapies that are considered part of complementary and integrative medicine. The term "massage therapy" encompasses a wide array of techniques. The following are some specific techniques that have been studied:

Traditional or classic massage – It can include deep tissue massage, segmental massage, with or without trigger point pressure in certain regions of the body.

Lymphatic drainage – It is a form of gentle massage that encourages the movement of lymph fluids around the body.

Traditional Thai massage (TTM) – It typically uses gentle pressure and stretching techniques to relax the whole body. Rather than passively lying on a bed, the person receiving the massage lies on the floor and actively participates in the massage. TTM can be divided into two types: the popular-type traditional Thai massage and the court-type traditional Thai massage (CTTM). In CCTM, pressure is applied on specific points along the meridian lines using polite gestures since it was used for royal families [17].

Reflexology – It is performed by applying pressure on the "reflex zones" of the feet that claim to correspond to the internal glands and organs of the body [18].

What Is the Mechanism of Massage?

Currently, the evidence for the therapeutic effects of massage for headache is limited. However, there is growing evidence that massage may have effects on physiological processes that contribute to the development of migraine. Some findings suggest that massage can influence a variety of stress responses by causing a shift from a state of sympathetic activation to a state of parasympathetic activation [19]. Stimulating the relaxation response can thereby reduce stress-related responses such as anxiety that can trigger migraine attacks. Massage therapy can also have effects on body pain and muscle tension that may contribute to migraine in some individuals. On a biochemical level, massage alters levels of serotonin and substance P [20]. Massage therapy can reduce muscle tension by breaking down subcutaneous adhesions, preventing fibrosis, and promoting circulation of blood and lymph [21].

In reflexology, it has been claimed that detoxification occurs by pressing the "reflex zones," which can remove energy blocks or lead to the elimination of disturbances such as calcium, lactate, or uric acid crystals. It has also been suggested that reflexology may help improve the body's blood flow and help release stress and tension [22].

The Evidence for Massage Therapy and Treatment of Headache

Upon reviewing the existing literature, it is evident that there is significant heterogeneity in the protocols used across studies of massage therapy for headache. In one of the few randomized controlled trials (RCT) of massage therapy for migraine treatment, 13 adult patients were randomly assigned to receive two 30-minute massages per week for 5 weeks. When compared with the control group, the massage group experienced fewer symptoms, lower anxiety levels, and more headache-free days over the 5 weeks. Massage participants, compared with control participants, rated the pain as milder and used fewer analgesics during a migraine attack [23]. After the last session, salivary cortisol was lower and urinary serotonin (5-HIAA) higher than baseline levels. However, there was no follow-up of patients after the last session; thus, the duration of massage effects is unknown [23]. In a larger RCT from 2006, 47 migraine patients were randomly assigned to massage or control conditions for 13 weeks [24]. The protocol was specifically designed for the treatment of migraine using a neuromuscular and trigger-point framework of the back, shoulders, neck, and head. Compared to control participants, massage participants experienced a greater decrease in migraine frequency and greater improvement in sleep quality during the intervention weeks and at 3 week follow-up.

In addition to the studies focused on migraine patients, there have been a few studies that have examined the effect of massage on chronic pain and other types of headache, such as tension-type headache. In an RCT of 29 patients with chronic pain, including headache, patients underwent ten sessions of 20 minutes of classic massage over 5 weeks. Massage was compared to standard medical care. The study found no significant difference in pain after treatment with massage. However, the massage group had persistent pain reduction paired with controls at 3 month follow-up [25]. In a 2014 RCT of 72 patients with tension-type headache and migraine, patients underwent nine sessions of traditional Thai massage over 3 weeks. Massage was compared to nine sessions of sham ultrasound control. Both groups experienced a decrease in headache intensity and frequency compared to baseline, but results were not statistically different between groups [26]. A 2015 study found that court-type Thai massage (CCTM) was an effective treatment for chronic tension-type headache. Sixty patients were divided into control group (prescribed Amitriptyline 25 mg for 4 weeks) and CCTM group (45 minutes, twice a week, for 4 weeks). Results demonstrated a significant decrease in Visual Analog Scale (VAS) pain intensity for the CTTM group [27].

Lymphatic massage is a form of gentle massage that encourages the movement of lymph fluids around the body. In a 2016 RCT, Happe et al. studied 64 patients with migraine who were randomized into three groups: Lymphatic drainage (LD), traditional massage (TM), and waiting group (WG). A treatment period of 8 weeks was followed by a 4 week observation period. The primary outcome measure was

migraine frequency per month. There was a statistically significant difference between LD and control group and TM and control group. LD was more efficacious in some parameters (such as a decrease in analgesic intake) compared to TM [28].

The effectiveness of foot reflexology for the treatment of headache remains in question as evidence is limited. A pilot study from 2017 evaluated the effects of foot reflexology versus segmental massage in reducing migraine pain intensity, frequency, and duration of attacks in 48 women [29]. In the reflexology group, the participants received a series of 10 treatments twice per week. In the segmental massage group, the participants received a series of 15 treatments three times per week. Results showed that foot reflexology and segmental massage decreased relapse rates and reduced symptoms of migraine attacks immediately following treatment and continued for 3 months. There was also a statistically significant difference between foot reflexology and segmental massage in the efficiency of reducing migraine symptoms. Women who underwent foot reflexology achieved significant improvement in all outcome measures, including VAS, headache intensity, frequency, and duration of attacks.

Recommendation for Patients Regarding Massage Therapy

Patients will often experience immediate benefits, but long-term benefits of massage require further research. In clinical practice, physical therapy is typically a long-term therapy recommended for management of myofascial muscle pain, which can be a contributor to ongoing headaches.

In terms of safety, a 2003 article in Rheumatology concluded that massage is not entirely risk-free, although serious adverse events are rare [30]. In case reports and case series, the majority of adverse effects reported were associated with exotic types of manual massage or massage delivered by a non-certified practitioner. These adverse events included hematoma, nerve injuries, pulmonary embolism, ruptured uterus, strangulation of the neck, cerebrovascular accidents, and displacement of a ureteral stent.

Tai Chi

Introduction

Tai Chi is a form of traditional Chinese mind-body exercise that has been practiced for hundreds of years in China and continues to be practiced by over 100 million people regularly in China alone [31]. In recent years, this slow and gentle form of exercise and meditation has been practiced widely throughout the world. To better understand Tai Chi, it is important to define the practice of Qi Gong. Qi Gong refers to the traditional Chinese practices involving the circulation of energy or "Qi" in pathways through the body. Tai Chi is technically a martial art that was developed from and based in Qi Gong practices. Therefore, Tai Chi is considered

a form of Qi Gong. Tai Chi combines breathing, coordination, relaxation, and mental focus to rebalance the body's healing capacity. Based on the philosophy of yin and yang, Tai Chi consists of slow movements that enhance posture and center of gravity. These movements are supported by deep breathing and meditation. The ying-yang symbol for Tai Chi represents the harmony between yin and yang. Yang represents the sun and aggressiveness, whereas yin represents shade and tranquility. The balancing nature of Tai Chi has traditionally been compared to the sun moving over the sky, with yin and yang exchanging positions with one another, illuminating what was previously hidden, and covering what was previously known [32].

The Evidence

Tai Chi is an evidence-based treatment for a variety of conditions, including prevention of falls in the elderly [33], lowering of high blood pressure, and improving mental health [34, 35]. Tai Chi has been found to improve exercise capacity, sleep stability, and quality of life in heart failure patients. There are very few prospective studies on the effect of Tai Chi for the treatment of headache. In a 2006 RCT of Tai Chi for tension headaches, 13 participants in the intervention group received one-hour, bi-weekly sessions of Yang style Tai Chi short form for 15 weeks. Classes were taught at a local park, away from the location of study assessment. Handouts that summarized the Tai Chi movements were given, and a video of the form was also provided to assist participants. The rest of the 17 participants were randomized to the waitlist control group. At 15 weeks, the intervention program of Tai Chi (Yang style short form) resulted in a statistically significant improvement of generic health outcomes for people with tension-type headache [36].

How It Is Practiced

There are different styles of Tai Chi, but most forms share a low-impact nature. The most widely practiced style of Tai Chi is the Yang style short form, which consists of 24 standardized movement forms [31]. In a typical session, participants plant their feet into the floor and turn the whole body in slow and fluid movements, using their waist as the center of gravity. A calm, peaceful mind must be maintained during the movements.

Classes at community and healthcare facilities are becoming increasingly prevalent and accessible. Patients can also choose to practice Tai Chi in the privacy of their homes by using Tai Chi videos. Most of the studies that illustrated positive benefits from Tai Chi therapy were for 12 weeks, two to three times a week [37].

Other Advantages of Tai Chi

The advantages of Tai Chi include the low occurrence of side effects, low cost, and the lack of specialized equipment. Tai Chi can be practiced anywhere and in most people, as it is a low impact activity. Additionally, Tai Chi addresses stress, which is often a significant underlying contributor to pain and headache. Overall, Tai Chi is a safe and gentle form of alternative exercise that could be a good fit for patients with chronic illnesses who want to improve their physical function and quality of life.

Yoga

Introduction

Yoga is an ancient mind-body intervention that includes sequences of postures, breathing patterns, and meditation that promotes relaxation. Yoga encompasses physical, mental, social, and spiritual factors that can influence health and disease. In addition to *ayurveda* (an ancient system of Indian medicine), yoga has been used for the management of various ailments for thousands of years. The principle behind *ayurveda* and yoga is that health is defined as a state of well-being resulting from a synergistic balance in principal systems' functions (*doshas*), body tissues (*dhatu*), excretory products (*mala*), and digestive fire (*agni*). Maintaining a state of good spirit (*atma*), sense organs (*indriya*), and mind (*manas*) is essential to achieve a state of good health [35]. For the purpose of this review, we will focus on yogic literature; however, it is important to bear in mind that *ayurveda* and yoga are intertwined (yoga is encompassed within *ayurveda* as a remedy) and often practiced together.

Migraine headache is referred to as *ardhavabedhaka* (under the classification of diseases of the head region) in *ayurvedic* literature [38]. The onset of *ardhavabedhaka* is attributed to a variety of causes, including fasting, alcohol, crying, daytime sleeping, anxiety, fear, and grief, amongst other factors. The remedy consists of a wholesome and regulated diet and lifestyle (*pathya ahara* and *vihara*, respectively). According to yoga, migraine is considered as a mind-body disorder (*adhija vyadhi*) where the disturbances in the mind influence the flow of the "vital force/breath" (*prana*), resulting in physical problems and affecting the weakest system in the body [39].

According to yogic literature, namely, the *hatha yoga pradipika*, food should be taken in moderate quantities and be pleasant and sweet, leaving one-fourth of the stomach empty. Foods to be avoided are those that are sour, pungent, or hot, such as mustard. Additionally, fish, meat, reheated foods, salty foods, alcohol, and curds (cheese) are to be avoided [40]. Eating foods that are not recommended may trigger disease states and aggravate *pitta* (a force that refers to the heat, metabolism, and digestion in the body), the principal factor in the onset of headache [41].

The literature mentions the existence of five stress-producing factors called *kleshas,* which are responsible for the onset of pain (*dukha*), which is physical or mental. Various diseases can be overcome through the regulation of mental modifications via practices involving maintenance of a positive attitude, breathing techniques, and meditation [39], along with adhering to specific ethical observances (*niyamas*). These observances are the following: purity of body and mind, mastery over the senses, and capability for self-realization (*shaucha*); contentment which brings joy and happiness from within (*santosha*); the concept that through training brings destruction of mental impurities and mastery over the body and mental organs of senses and actions (*tapah*); and self-study and reflection on the sacred (*svadhyaya*). Through the practice of these observances, one can attain a state of perfect concentration (*Samadhi*). Disease may occur if one does not practice the above observances (*niyamas*), along with ethical living that incorporates principles of nonviolence, non-greed, and living in a state of awareness (*yama*) [42].

There is a concept of therapeutic yoga, which is explained in the *Gita*, a Hindu sacred text. The literature describes that one who adheres to the right diet, lifestyle, actions, and regulated sleeping and waking hours can mitigate pain and disease through yoga [43]. Yoga emphasizes healthy and nourishing food for the management of illness, control of the mind through yoga, moral-ethical living, and the idea that the body has an internal healing capacity, which can be enhanced by the practice of *yama* and *niyama*. The practice of various physical postures (*asanas*) and regulated breathing exercises (*pranayama*), cleansing (*kriya*), meditation, and relaxation techniques are used in the management of all disease states, including headaches.

The Evidence

It is important to keep in mind that yoga is challenging to study systematically given the diversity of practice, providers, and cultural approaches to incorporating a yoga lifestyle [44]. In one RCT of yoga in patients with migraine without aura ($n = 72$), the practice of yoga 1 hour daily, 5 days a week, for 3 months, significantly decreased headache frequency, pain index, and symptomatic medication use compared to a self-care group [45]. The principal limitations of this study were that the yoga protocol used was not revealed and that participants were instructed to only practice yoga during the prodromal phase of the headache [46]. Another RCT ($n = 60$) took patients with migraine with or without aura and compared yoga practice 5 days a week for 6 weeks with conventional care control. When compared to controls, yoga was found to significantly reduce monthly headache frequency, VAS score, and headache impact test (HIT-6) score [47]. A small non-randomized controlled trial of patients with chronic tension-type headache compared medication (non-steroidal anti-inflammatory drugs; NSAIDs), botulinum toxin, and yoga (2 weeks of yogic lifestyle training followed by 2 weeks of home practice) with a matched control

group. Four weeks after the interventions, VAS scores improved in the NSAIDs group and yoga group but not in the botulinum toxin group [48].

It should be noted that the data on yoga for chronic pain and headache comes from studies performed in India, where the yogic practice is culturally prominent [44]. Patients may have had other aspects of lifestyle management not accounted for, including a particular diet and meditation or ayurvedic practices. Furthermore, the studies involved patients who practiced yoga for 3 to 4 hours or more a week without provoking postures, such as prolonged bending [44]. Further large-scale randomized studies on yoga are needed with a focus on detailed protocol, including what type of yoga is being practiced and the qualifications of the instructors. Particular consideration should also be given to other lifestyle measures that likely play a role, including regular sleep, diet and exercise (or lack thereof), and, given the particular population, what cultural practices predominate. Thus far, the data collected from the few conventional studies lack details regarding physical limitations (such as in the elderly and disabled), as well as simultaneous medication use.

The Benefits of Yogic Practice

There are multiple benefits to a regular practice of yoga. These include improved quality of life through calming and focusing the mind to develop greater awareness, which can diminish anxiety [49] and distress [50]. Yoga has also been shown to increase physical flexibility, coordination, and strength [51]. These practices increase the patient's self-awareness of the possibility of being physically active despite pain symptoms. Patients may feel a higher sense of self-competency and self-awareness, which contributes to an improved quality of life [52].

Introducing Patients to Yoga

As a clinician, it is challenging to guide patients when it comes to yoga for headache management. There remains a lack of data regarding what specific types of yoga are most effective for headache treatment. As mentioned previously, the majority of studies have been conducted in India, where yogic practices are culturally prevalent. Should patients be interested in starting a yoga lifestyle, clinicians may consider directing them online to find yoga centers in local areas that may offer more comprehensive yogic teachings. It is important to gain such teachings from reputable sources as improper yoga practices may cause physical or mental harm. Other considerations around successfully implementing yoga include awareness of the type of headache syndrome and triggers a patient has, such as bending over, laughing, or coughing, which may be practiced in some types of yoga.

Behavioral Medicine

Introduction

Behavioral medicine is an interdisciplinary field that recognizes that biological, psychological, and environmental factors play a significant role in how humans function [53]. The behavioral medicine approach to the treatment and management of headache can be divided into categories of behavioral treatments, including cognitive-behavioral therapy (CBT) and biobehavioral training (biofeedback, muscle relaxation, and stress management), as well as physical therapies and education including lifestyle modification [54]. Behavioral medicine therapies may be used individually or in conjunction with other pharmacologic therapies.

The formation of The United States Headache Consortium was created expressly to provide guidelines regarding headache treatment modalities. As per the consortium, the primary goal of behavioral interventions is for the preventative treatment of headaches; however, some of the interventions may also be utilized as an abortive method. The goals were to decrease the frequency and severity of headaches, headache-related disability, reliance on poorly tolerated or undesired pharmacotherapies, headache-related distress, and psychological symptoms [55]. The underlying purpose of intervention was to enhance one's personal control of migraine. It is worthwhile to mention that per the guidelines, there is Grade A evidence for the use of relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and CBT [55]. There is Grade B evidence supporting behavioral therapy combined with preventative drug therapy to achieve added clinical improvement for migraine [55]. The focus of this review will be on biobehavioral training, specifically biofeedback and progressive muscle relaxation.

Biofeedback

What Is the Mechanism of Biofeedback?

Biofeedback is a procedure that monitors the physiological processes that patients may or may not be aware of or feel that they have any voluntary control over [54]. The training increases a patient's awareness of these physiological processes in attempts to regain voluntary control over these processes. The practice of biofeedback involves teaching patients various relaxation skills, such as diaphragmatic breathing or visualization, to induce relaxation [56]. The biological or physiological information that is collected is then converted into a signal that is "fed back" to the patient through a computer monitor and often with some audio input [54]. There are several biofeedback modality options, including peripheral skin temperature feedback or thermal biofeedback, blood-volume-pulse feedback, electromyographic feedback, galvanic skin response training, or skin conductance feedback and electroencephalographic feedback of alpha waves [54].

Of the various modalities, thermal feedback has the most evidence for efficacy in the prevention of migraine [55]. The experience of pain pushes the body to enter a state of sympathetic activation or "fight or flight." In this state, the extremities receive less circulation, which can lead to a decrease in temperature. When the body begins to relax, the parasympathetic system will act conversely, causing increased circulation to extremities, which leads to an increase in temperature in the extremities. With thermal feedback, patients will have their finger temperature monitored with a sensitive thermometer; higher finger temperatures correspond to states of greater relaxation.

The literature on the neurophysiology of migraine and functional MRI studies of pain networks suggests that behavioral interventions may affect neuromodulation [57]. According to other studies, it was reported that relaxation training and thermal biofeedback could produce as much as 33–37% improvement in headache activity [55]. In one systematic review of biofeedback in headache that assessed 94 studies with more than 3500 patients, peripheral skin temperature feedback, blood-volume-pulse feedback, and electromyography feedback showed a significant, medium-sized effect on headache frequency, intensity, and duration in patients who received the treatment [58]. Another pilot RCT of biofeedback compared 25 patients who were diagnosed with migraine and lacked psychiatric conditions to 22 waitlist control patients. Real-time data was recorded on a handheld device for 4 weeks before and after treatment. The study found that there was reduced headache intensity after biofeedback compared to the control group [59].

Treatment Course

Biofeedback is administered by trained psychologists, medical professionals, or mental health professionals. Clinicians can direct patients to search online for a local, certified biofeedback provider. A patient should expect to receive treatments over an average of 8–12 sessions that are one to several weeks apart [54]. During the sessions, patients will learn coping strategies such as relaxation skills. In between sessions, they are expected to continue to practice these techniques for manipulation of basic physiological processes to induce states of relaxation, which can help regain control over their pain experience. As the patient demonstrates an increasing ability to conduct this process, the biofeedback device may be eliminated [54].

Progressive Muscle Relaxation

What Is the Mechanism of Progressive Muscle Relaxation?

Relaxation techniques work by minimizing the physiologic response to stress; decreasing sympathetic arousal is a key objective [54]. The most common types of relaxation training used for the treatment of headache are progressive muscle

relaxation (PMR), autogenic training, and meditative or passive relaxation [60]. PMR was first reviewed in 1938 by Edward Jacobson at the University of Chicago. PMR involves the tensing and relaxation of various muscle groups while taking note of the sensations it produces [61]. Jacobson's studies on muscle relaxation led him to conclude that tension arose from the effort manifested in the shortening of muscle fibers when a person reported anxiety. He found that relaxation of muscle fibers was the physiological opposite of tension and, therefore, a logical treatment for a person with tension. He discovered that systematic tensing, as well as releasing of muscle groups and recognition of the sensation felt with each, could help a person eliminate muscle contractions and experience deep relaxation [62].

Treatment Course

The training is typically delivered by a physical therapist who explains the procedure of relaxation of 16 muscle groups to the patient. Per traditional teaching, it is important to be consistent with the order in which the muscle groups are relaxed. The following is the order in which muscle groups are addressed [62]:

1. Dominant hand and forearm
2. Dominant biceps
3. Nondominant hand and forearm
4. Forehead
5. Upper cheeks and nose
6. Lower cheeks and jaws
7. Neck and throat
8. Chest, shoulders, and upper back
9. Abdominal or stomach region
10. Dominant thigh
11. Dominant calf
12. Dominant foot
13. Nondominant thigh
14. Nondominant calf
15. Nondominant foot

For each muscle group, the patient's attention should focus specifically on that muscle group. At a predetermined signal from the therapist, the patient will tense the muscle group and maintain this tension for 5–7 seconds (or less in case of the feet). At a predetermined cue, the patient will release the muscle group. The patient focuses attention upon the muscle group as it relaxes. The 15 muscle groups are often tensed and released twice to assure complete relaxation under a therapist's verbal and sometimes physical guidance [62]. Patients should practice these techniques at home and in between sessions.

Patients can find many resources online about PMR, which can allow them to learn and practice PMR techniques on their own successfully. The order in which muscle groups are addressed may differ among various sources, and, without the education from a trained therapist, efficacious tensing and relaxation of muscles may not occur consistently and therapeutically.

Mindfulness Meditation

What Is Mindfulness?

Mindfulness has ancient roots that are grounded in Hinduism, Daoism, and Buddhism. The underlying concept of mindfulness is that there is an intentional, non-judging mental awareness on the present in order to control the effect of mental activity on physiological processes [63]. The premise is to draw attention to internal sensations, including pain and emotion, and intentionally alter one's response in an attempt to enhance functioning. In other words, it seeks to break patterns of mental and emotional response to a given stimulus that may be of detriment to the self.

When it comes to the modern application of mindfulness for pain or stress relief, one of the most popular forms of practice is through mindfulness-based stress reduction (MBSR) [64]. MBSR courses adapted for headache patients are typically composed of eight weekly, two-hour group sessions, in addition to a final day consisting of a "mindfulness retreat," lasting approximately 6 hours. Patients can enroll in courses taught locally or even participate in an online MBSR course. Some techniques taught include mindful eating, breathing, sitting and walking meditation, body scanning, and yoga for mindful movement. The participants in the program share their experiences and are taught strategies for stress relief through various learned techniques. Participants are also continually reminded to bring their attention back to more natural patterns of breathing. After being taught how to bring mindfulness into routine activities, including brushing teeth and showering, participants are encouraged to continue these practices in their everyday life.

MBSR for the treatment of various recurrent stress and pain states has been the focus of several studies in subsequent years with the primary goal of minimizing the focus on pain by avoiding the impulse to "fight it" [63]. One of the first RCTs with episodic migraineurs ($n = 19$) was conducted by Wells and colleagues and published in 2014. In this trial, patients were assigned to usual care (mainly pharmacological prophylaxis) or usual care combined with MBSR. Although the addition of MBSR did not alter headache frequency (primary outcome), it did lead to an improvement in many secondary measures including headache duration, disability, self-efficacy, mindfulness, and HIT-6 score [46]. The study had limitations, namely, the small sample size, which limited the ability for randomization to balance groups at baseline.

How Do Mindfulness-Based Therapies Work?

The exact mechanism of how mindfulness works in regulating pain is controversial. There is much that is unknown and likely involves a complex psychophysiological state in which patients examine their experiences of pain and concurrently modify their reactions to it. Potentially, the exercises involving mindfulness help to develop the patient's internal locus of control. Observing a decrease in symptoms can help to build self-esteem and the concept of self-efficacy [63]. Interesting studies have been done in recent years that have utilized functional magnetic resonance imaging (fMRI) to study cerebral circuits involved in pain processes. In one such study, Grant and colleagues conducted fMRI on patients who regularly practiced meditation and compared the results to those who did not practice meditation. They found that, during the presence of pain, experienced practitioners had reduced activation in the amygdala, hippocampus, and emotional/evaluative regions of the prefrontal cortex, as well as increased activation in the mid-cingulate cortex and insula. These results provide evidence that mindfulness allows one to increase attention to the present experience in order to decrease the emotional response [65]. When evaluating the data from neuroimaging studies for meditation through mindfulness, it is clear that there is a down-regulation of anticipatory representation of aversive events and an increase in the recruitment of attentional resources during the experience of pain. These changes are associated with quicker neural habituation [66]. With the knowledge that mindfulness training and meditation impacts brain areas connected to neuromodulation and the control of pain, the evidence is building in support for mindfulness-based approaches in the treatment of recurrent headache.

Conclusion

Mind-body therapies serve as a helpful set of tools for some patients who experience headaches. Given the wide array of options, it can be challenging for clinicians to determine which therapies to recommend to their patients. In general, patient safety should always be the top consideration. The next consideration should be patient preference. It is imperative that the patient feels comfortable with the therapy and can access it. Sharing the evidence behind these therapies with the patient can help inform their final decision. In the therapies discussed in this chapter, biofeedback has the highest level of evidence for the treatment of headache. There is growing evidence that acupuncture can be effective in treating migraine and tension-type headache. There is currently very little evidence for the use of mindfulness meditation, progressive muscle relaxation, massage, tai chi, and yoga for the prevention and treatment of headaches.

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Chapter 8
Psychology of Headaches

Joy J. Choi and Craig L. Katz

Introduction

Headaches are complex physiological and psychological phenomena. A headache can serve as a manifestation of psychological distress and can also in and of itself cause psychological distress. Although there has yet to be solid evidence demonstrating the causal linkage between a specific headache disorder with a psychiatric disorder, it is undeniable that headaches are closely linked to psychiatric disorders and various psychological states. This chapter aims to provide an overview of the psychology of pain and its implications for headache disorders. It also explores the common psychiatric comorbidities for headache disorders, including stress and trauma, anxiety disorders, mood disorders, alcohol use, somatoform disorders, and schizophrenia. Of these comorbidities, this chapter focuses primarily on the mood and anxiety disorders in terms of screening and management of psychiatric comorbidities in headache patients – both pharmacological and behavioral.

Psychology of Pain

A discussion of the psychology of headaches can be traced back at least as far as Sigmund Freud, who himself suffered migraines and directed some of his theorizing to understand their etiology [1]. His ideas evolved greatly over time from such ideas

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as "nasal-reflex neurosis" in which the cause was felt to be hypertrophic nasal tissue, to migraines' relationship to proneness, to narcissistic insult, to ones that would seem more familiar to us today, especially the conversion of unconscious conflict into somatic symptoms. Freud's far-ranging ideas in many ways foreshadowed the reality of modern-day psychological concepts of headache, namely that there is as yet no unified psychological understanding of headaches but instead a range of ideas and findings of variable significance and clinical relevance. Many of these ideas might ultimately be best judged by their clinical utility from patient to patient, circumstance to circumstance, and possibly headache type to headache type.

We have divided the extant psychological literature on headache and pain into three broad areas for purposes of this chapter, as follows: (1) personality types and headaches; (2) attachment theory and pain; and (3) broad psychological concepts.

Personality Types

The idea that headache sufferers manifest certain personality styles has much cultural currency, and research has provided at least some evidence base in support of this. However, much of the research dates back decades and may require further study to more rigorously address the connection between headache and personality.

A 1974 study of government workers in England found that migraine sufferers were more likely to be neurotic, anxious, and prone to somatization than other headache sufferers and in controls with no headaches [2]. Being neurotic or having a neurosis derives from Freud's term, psychoneurosis, and reflects a disturbance that derives from intrapsychic conflict and impairs functioning without causing a disturbance in reality testing as would psychosis but instead manifests as anxiety, hysteria, or obsessing [3, 4]. The subjects were also less likely to be extroverted. Subjects attending migraine clinics, in particular, were generally more likely to exhibit hostile behavior and attitudes.

On the other hand, a somewhat later study examining personality profiles in patients with cluster and migraine headaches not only found no difference in personality profiles between the two groups but also found no evidence of neuroticism [5]. Another study examining cluster and migraine headache sufferers using the Minnesota Multiphasic Personality Inventory (MMPI) likewise found little or no psychopathology in subjects with migraine or cluster headaches [6].

Proneness to fear of pain, fear of feeling anxiety, and tendency to avoidance may account for the general association of chronic headaches and psychiatric conditions [7]. And reviews of studies on headache and personality found that, altogether, headache sufferers in general and also migraine sufferers, in particular, are more prone to have neurotic personalities [8, 9]. However, these studies often did not control for confounding factors such as headache frequency, other psychiatric disorders, or clinic versus community samples [9]. And the conclusion of the author of one of the studies is noteworthy as it seems to be as true now as it was in 1975:

> There is very little doubt in my mind that people with headaches perform differently on psychological tests than non-headache controls. There are a number of plausible

> explanations for these findings, only one of which is the etiological hypothesis that is so tempting to accept. The differences may be there because psychological factors cause or predispose people to have headaches. The differences may also be explained as a consequence of chronic exposure to the risk of sudden intense pain [8].

Going beyond the psychology of personality to the more severe personality disorders, migraine, and severe migraine headaches are especially prevalent in patients with borderline personality disorder and, to a lesser degree, obsessive-compulsive personality disorder, and avoidant personality disorder [10, 11]. They may also associated with medication overuse. The latter two disorders, in so far as they are what is commonly considered part of the "anxious" cluster of personality disorders would be consistent with prior findings of an association between neurotic personality styles.

Attachment Theory

Attachment theory posits that healthy human development relies on the consistent and reliable presence of an infant's primary caregivers, especially in times of distress. How well caregivers meet this need will determine not only the infant's immediate sense of security in the face of stress but their lifelong capacity for establishing this sense [12]. Not surprisingly, attachment theory has been used to understand human reactions to the stress of illness, including how the afflicted individual relates to and elicits the ministrations of health care providers. In this vein, chronic pain, and by corollary, headaches, can be understood through the lens of attachment theory [13]. "Pain complaining" has been described as an attachment behavior by which the sufferer elicits responses from caregivers [14]. Insecurely attached individuals are theorized to be more prone to chronic pain, less able to manage it, and less proficient at recruiting help from supports and health professionals. And empirical studies have revealed that insecurely attached individuals deal with chronic pain in a more emotion-focused and less problem-focused manner. Therefore, according to the attachment diathesis model of chronic pain, the extent to which an individual is securely attached will influence three key appraisals that together presage their eventual adjustment to the pain and overall well-being, namely appraisal of the pain itself, of their self-efficacy, and of the availability of social support [12].

Clinical experience, as well as theory, suggests that four styles of attachment will influence how people with pain, such as headaches, cope, and especially how they help seek [13]. People with *secure attachment* can effectively seek out help from healthcare professionals and support from people around them. They are less prone to develop problems with chronic pain.

Individuals who have *dismissing attachment* tend to respond to threats such as pain by withdrawing and avoiding help-seeking, dismissing both the pain and the capability of others to help them. This dismissal can manifest in a tendency to superficially seek out multiple health professionals for help with headaches but without establishing a therapeutic relationship with any of them. They thereby dismiss their recommendations, which in turn may worsen their pain, leading them to further criticize and distance themselves from help and so forth in a vicious cycle.

People with *fearful attachment* distrust other people and concomitantly have a sense of self as unworthy of help. Much like people with dismissing attachment, they are likely to delay seeking help for their pain until they are desperate and present a sense of helplessness and hopelessness than can overwhelm their doctor. They may then respond minimally to receiving care, possibly being ambivalent about relinquishing their pain due to their deeply held doubts about whether they deserve to feel better.

Finally, patients with *preoccupied attachment* are both help-seeking and help-rejecting; the latter deriving from a fear of being rejected and being withdrawn from them. Typically, initial responses to treatment and support give way to a rejection of treatment recommendations as the patient becomes ambivalent about accepting help for fear they will fail and disappoint as a patient. They may unwittingly sabotage treatment and move from doctor to doctor in hopes of breaking this pattern, essentially "quitting before they're fired."

A fascinating concept related to attachment and interpersonal theory is that of the "headache model." In a small study, researchers found that chronic headache sufferers were significantly more likely than non-sufferers to report having had a family member who frequently complained of headaches [15]. This study replicated findings in other pain patients but did not control for such factors as genetic inheritance and did not spawn follow-up studies that did. Nonetheless, it suggests at least the intuitive possibility that caretakers may model future pain management and even experience, presenting a potentially clinically useful construct.

Broad Psychological Concepts of Pain

The emotional and evaluative components of pain are significant contributors to how much pain someone feels [16]. There are several dimensions to this which bear on headaches. First, the *context* in which pain is experienced matters greatly, as can be seen in the case of a soldier who suffers a major combat injury but experiences mild pain. Second, focusing *attention* too much on pain makes it worse, while distraction can have mitigating effects. Third, anxiety and a *sense of loss of control* worsen pain, which perhaps is best reflected in the salutary effects of patient-controlled analgesia. Fourth, as in the suggestive case of headache models, pain can be a *learned response*. Fifth, patients' *expectations* of how much pain they should feel can influence the extent of their pain, their response to treatment, and whether it becomes chronic or disabling. Finally, *behavioral responses* to pain can make them worse, creating a vicious cycle in which the worsened pain perpetuates unhelpful behavior, as exemplified by medication overuse by headache sufferers.

To elaborate further on behaviors, although non-pharmacological treatments such as relaxation training and biofeedback exist for headaches and may be no less effective than medications, there is considerable non-adherence with non-pharmacological/behavioral prescriptions [17]. These behaviors include readiness for change, awareness of triggers, locus of control (internal vs. external), and sense of self-efficacy. Regarding readiness for change and engaging in "change behavior," patients exist on a continuum from pre-contemplation of change, to contemplation, to preparation for

change, to action, and finally to maintenance. Meanwhile, patients who possess an internal locus of control and thereby trust in their ability to influence the world around them are much more likely to adopt behavioral prescriptions for headaches.

Other psychological dimensions that influence the perception of pain beyond its physical perception relate to the consequences of the pain [18]. There is the extent to which it *interrupts* moment-to-moment attention and behavior. It also *interferes* with completing tasks effectively. And, pain, perhaps especially when it is chronic, affects one's sense of *identity*. This not only bears on who one was in the present but on the sense of who one can be in the future.

Psychiatric Disorders

A range of psychiatric disorders has been consistently associated with chronic pain, chronic headaches, and chronic migraine [7, 19, 20]. For now, this association can only be said to be correlational, although further research may yet find more unidirectionality. Psychiatric disorders generally tend to worsen the prognosis of headaches, for example, leading to the "chronification" of migraine [7]. They also contribute to treatment resistance, medication overuse, and worse quality of life for the headache sufferer. Meanwhile, chronic pain and headaches are associated with higher rates of psychiatric conditions and can likewise affect their course. Although pathophysiological explanations for the bidirectional nature of headaches and psychiatric conditions remain to be determined, possible mechanisms include shared serotonergic dysfunction, medication overuse, and psychological factors noted earlier, such as proneness to fear of pain, fear of feeling anxiety, and tendency to avoidance [7].

Here we will review the association between headaches and specific psychiatric disorders.

Stress and Trauma

Although not a disorder per se, stress is a frequent concomitant of psychiatric disorders. Stress, defined as a state of imbalance between physiological, environmental (including interpersonal or other life events), or psychological stressors and coping strategies associated with discomfort or unease, is likewise frequently associated with headaches. Stressful life events have been shown to lead to the onset of migraine, to trigger migraine attacks, and to cause migraine chronification. And, migraine headaches themselves constitute a physiological stressor that can perpetuate stress-migraine cycles [21].

Stress is considered perhaps the most commonly reported trigger for migraine attacks, although attacks may occur more frequently after the "let down" periods following stress [22]. For example, one study found that approximately half of migraine sufferers experienced their first migraine during a period of stress, while 20–40% of respondents with migraine without aura reported getting migraine attacks during lower stress times compared to 12% of subjects with non-migrainous

headaches [2]. Among environmental stressors, however, it may be that daily "hassles" rather than major life events are more highly correlated with frequency and intensity of chronic headaches, especially tension or mixed headaches [23].

Trauma may be broadly considered on a continuum with stress, constituting a severe stress that overwhelms the individual's coping abilities, and begets a pathophysiological and psychopathological state. Studies of trauma and post-traumatic stress disorder (PTSD) have found correlations with headache, although some have only seen this association in clinical samples or in women. Findings of whether there is an increased prevalence of trauma in headache sufferers have been inconsistent. In the end, however, there are consistent findings that, like other psychiatric disorders, PTSD contributes to greater headache-related disability [24–26].

Anxiety Disorders

Perhaps not surprisingly, given the associations between neurotic personality traits or stress and headache, anxiety disorders are among the class of psychiatric conditions most commonly associated with headaches [7]. Migraine sufferers are 3.7–6.6 times more likely to suffer from panic disorder, 5.7 times more likely to suffer from generalized anxiety disorder, 5.1 times more likely to suffer from obsessive-compulsive disorder, and 2.6 times more likely to have a diagnosed phobia [27, 28]. High rates of anxiety disorders have been found in both migraine and tension-type headache [29]. They contribute to greater costs of treatment, poorer treatment response, and chronification of headaches. Indeed, they are so common in headache sufferers and have such a deleterious impact on headache course and quality of life that it has been suggested that all patients with headache be screened for anxiety disorders [27].

Mood Disorders

The considerable prevalence of major depression in headache sufferers has likewise led to the recommendation of screening all such patients for this condition [27]. One study of patients with migraine or tension-type headache found a history of at least one major depressive episode in 59.9–69.6% of patients [29]. The bidirectional influence of psychiatric conditions and headaches is exemplified by depression. One study, in particular, found that having major depression at baseline predicted the onset of migraine at two-year follow-up with an odds ratio of 3.4 while having migraine at baseline predicted the onset of major depression at follow-up with an odds ratio of 5.8. These findings did not hold for severe non-migrainous headaches [30]. Major depression has also been associated with chronification of migraine, an association that increases with worsening depressive symptoms [31]. Potentially

aggravating the clinical picture further is the finding that clinical anxiety and depression have been found to co-occur in migraine sufferers frequently [32].

There is also considerable bidirectionality between bipolar disorder and migraine. A systematic review of the research literature found a mean 30.7% of patients with bipolar disorder suffered from migraine, whereas 9% and 5% of clinic-based or community-based migraine sufferers had bipolar disorder. These associations were strongest in women and bipolar II disorder [33].

Alcohol Use

Although alcohol has long been regarded as a trigger for migraine attacks, studies have not necessarily supported this. And we are not aware of studies that have examined alcohol use disorders rather than alcohol consumption.

While alcohol use has been reported as an occasional migraine trigger, some studies have found it is not reported as a consistent factor and that alcohol use may even be lower in headache sufferers than in the general population [34]. Prospective studies of alcohol use and migraine do not support its role as a trigger. They have tended to find that headache prevalence and frequency are inversely related to increased alcohol intake [35]. However, these findings may be the result of changes in alcohol intake in response to its triggering effect. Retrospective bias and confounding factors such as alcohol-related sleep disturbance may account for its being commonly ascribed as a migraine trigger.

Hence, moderate alcohol intake is probably not contraindicated in headache sufferers in general unless their particular experience or other contravening health issues dictate otherwise. However, consideration should be given to some evidence that wine, and especially red wine, can be a trigger for migraine and possibly other types of headache [36, 37].

Somatoform Disorders

There is surprisingly scant literature on the prevalence of somatization in headache sufferers. One available study found rates of various somatoform disorders in 21.6% of clinic attendees with tension-type headache, while finding 53.4% had anxiety disorders and 36.9% depressive disorders [38]. Another study of patients at a headache clinic found that patients with chronic migraine and chronic daily headache had significantly more somatic complaints than patients with acute migraine or primary care patients, and that the most commonly reported symptoms were sleep disturbance, and fatigue [39]. Adolescents with migraine have likewise been found to be more prone to somatization [40].

Schizophrenia

In a 1980 letter to the editor of the *American Journal of Psychiatry*, the authors shared their clinical experience that none of their patients with schizophrenia suffered from migraine headaches and expressed a since unfulfilled hope that such a striking finding might be helpful to elucidate the underlying biology of these conditions [41]. And a very recent review highlighted findings that patients with schizophrenia have a lower prevalence and intensity of chronic pain such as headaches and have higher pain thresholds and a reduced response to induced pain [20]. However, another review made the observation that studies actually reflect that schizophrenia sufferers have a heightened pain tolerance for pain associated with medical procedures, i.e., lumbar puncture, but not the pains of everyday life [42]. For example, a 2017 study of patients with schizophrenia found that their 12-month prevalence rate of headaches was 57% (higher than the general population), with tension-type headache occurring at a lower rate and migraine and cervicogenic headache occurring at comparable rates to the general population. They also found, as is typical of medical issues in schizophrenia sufferers, that none of them were receiving best-practice care for their headaches [43].

The conflicting findings regarding pain and headache in schizophrenia sufferers may be explained based on under-reporting of symptoms, which itself has not been elucidated [42]. Possibilities range from attenuated motivational aspects of pain experience that would be in keeping with amotivation that is often found in schizophrenia, altered cognitive processing, or possible analgesic effects of anti-psychotic medications. Altogether, it appears that headache diagnosis in schizophrenia may be challenging, but that many types of chronic headaches are at least as prevalent in these patients as in the general population.

Treatment Approaches: Behavioral Interventions

As discussed in the previous section, *Broad Psychological Concepts of Pain,* headaches can be associated with maladaptive behavioral patterns. These negative behavioral patterns create a vicious cycle of worsening headaches. Again, an example of this is medication overuse by headache sufferers. Therefore, it is not surprising that there is a growing body of literature studying the effectiveness of behavioral interventions for the treatment of headaches. In theory, it makes sense that interventions such as cognitive behavioral therapy, biofeedback, relaxation techniques, and/or a combination of these modalities would help reduce these maladaptive behavioral patterns, thereby reducing overall headache burden. However, the outcomes of many studies measuring the efficacy of these interventions are mixed. This section provides an overview of these studies and how to apply them to clinical practice.

An Overview of Behavioral Interventions

Behavioral interventions can be divided into two common categories: those that target physiological responses to headaches (i.e., biofeedback, relaxation techniques) and those that modify the maladaptive behavior, feelings, and thoughts in response to headaches (i.e., cognitive behavioral therapy). These interventions are built on the premise that the psychological and physiological components of headache are interdependent on one another. Common goals for these interventions include identifying headache triggers and acquiring skills for headache prevention [44, 45].

Unlike other behavioral interventions, biofeedback is unique in its utilization of equipment. It is performed by a trained specialist who uses monitoring devices to monitor the patient's physiologic function, including muscle tension, pulse, blood pressure, peripheral blood flow. The intervention allows the patient to observe what is normally an involuntary and/or unconscious bodily function. The equipment translates the physiologic response to audio or visual cues for the patient. The patient learns to use these cues to modulate the monitored physiological response [45]. A commonly used biofeedback type for the treatment of headache is the use of sEMG (surface electromyography) for tension-type headache [44–46]. In this type of biofeedback, the patient monitors his/her pericranial muscle tension, one of the suspected triggers for tension-type headaches. The biofeedback specialist then trains the patient to use certain exercises to reduce muscle tension. The monitor measures the reduction in muscle tension, then relays it to the patient. Using this feedback loop, the patient learns to reduce headache triggers effectively [46].

Biofeedback is often combined with relaxation techniques or cognitive behavioral therapy (CBT). The latter two can be the exercise used by the patient to try to lower physiological responses (i.e., muscle tension in case of tension headache) to prevent headaches [46]. Relaxation techniques include progressive muscle relaxation, autogenic training, guided imagery, and mindfulness. These are relatively easy to learn and, once mastered, can be utilized on one's own. The ability to independently practice these techniques, in turn, empowers the headache sufferers to actively manage their own physiological responses to decrease sympathetic arousal and decrease headache symptoms [44].

In progressive muscle relaxation (PMR), one intentionally tenses up distinct muscle groups, one at a time (i.e., hand, forearm, shoulder, hip, thigh, etc.), followed by the release of tension. The goal is to learn to distinguish the state of tension and relaxation in various muscle groups. Over time, it leads to reductions in skeletal muscle tension [47].

While PMR works on reducing skeletal muscle tension, autogenic training (AT) works to decrease autonomic arousal by working on smooth muscles (i.e., muscles of the cardiovascular system, abdominal muscles, etc.). In AT, the focus is on concentrating on words and images that evoke a state of desired physiological state. The participant is guided through verbal and visual sequences to achieve this goal. For

example, a patient suffering from migraine headache may be instructed to repeat phrases or images of "forehead and neck cool and relaxed." Over time, the participant would begin to feel that the forehead and neck are indeed cool and relaxed [47, 48]. Of note, AT requires a greater ability to concentrate than PMR and may work best for individuals who respond well to these suggestive phrases and images [47].

Similarly, guided imagery also requires a fair ability to focus on the exercise. Guided imagery involves a therapist verbally guiding the patient through a series of scenarios or images. Using these images, the therapist evokes a state of relaxation [47, 49]. For example, the therapist may guide the patient through a set of relaxing images (i.e., nature, traveling, etc.). Furthermore, there are anecdotes that guided imagery can be used to reduce headache directly. In his book, *Guided Imagery: Creative Interventions in Counselling & Psychotherapy,* the author shares an experience in which he used guided imagery for a colleague suffering from migraine headache. The colleague was asked to describe the migraine headache as an image. When it was described as a metal block, the author suggested the colleague imagine that it had now been taken by the author and placed in his pocket. The colleague reported the resolution of his headache after this exercise [49].

Mindfulness is also an exercise of concentration and internal reflection. However, unlike guided imagery, mindfulness does not focus on a specific chosen theme. On the contrary, mindfulness is a psychological state of openness, acceptance, and a non-judgmental stance toward any stimuli. It is a state of accepting and letting go of any thoughts, feeling, and sensations as they arise [47]. In headache sufferers, it can be a helpful tool to attenuate negative emotional responses to headache pain. Gradually this may also help foster a sense of internal locus of control over headache symptoms [50]. As mentioned previously in this chapter, an internal locus of control is associated with better adherence to behavioral interventions. In this way, mindfulness can be complementary to other behavioral interventions.

Cognitive behavioral therapy (CBT) differs slightly from biofeedback, PMR, and AT in that it does not aim to influence physiological responses related to headache directly. Rather, CBT is a highly structured type of psychotherapy in which the therapist and patient identify and modify potential triggers, problematic assumptions, and maladaptive coping skills. When applied to headache treatment, patients are asked to keep a headache journal which details information including thoughts and emotions preceding and following the headache, activities preceding the headache, duration and severity of headache, medication usage, and psychological coping skills used if any. By using this journal, a pattern of behaviors and thoughts that alleviate or worsen headaches can be identified. Through CBT, the maladaptive behaviors and thoughts are challenged, while the helpful ones are reinforced. For example, a headache sufferer may notice that his/her headache is frequently preceded by stress at work, which is precipitated by the irrational belief that one must be perfect and cannot make any errors. In this case, the therapist may challenge this belief and directly address the unrealistic perfectionism and subsequent anxiety that is contributing to headache symptoms in this patient [44, 51]. Lastly, CBT can be combined with other behavioral interventions.

Indications for Behavioral Interventions

Behavioral interventions are advantageous for certain headache patients. For example, patients who cannot tolerate medications, either due to side effects or contraindications, would undoubtedly benefit from non-pharmacologic treatment options. For example, patients who have concerns regarding taking medications while pregnant or lactating may consider the use of behavioral interventions. Additionally, patients who are at risk of medication overuse may also benefit from non-pharmacological treatment options [52]. There have been several studies suggesting that combining behavioral intervention with medications may provide more significant benefits than either modality alone [53–55].

In one study, patients with migraine and analgesic overuse were followed for 3 years after 10-day inpatient treatment. During these 10 days, patients were treated with pharmacotherapy alone or pharmacotherapy combined with biofeedback-assisted progressive muscle relaxation [56]. The study demonstrated that the group receiving combination therapy had a greater reduction in average headache days at 36 months (11.2 versus 18.1) and the number of analgesics consumed monthly (4.9 versus 20.1).

The same study also utilized the Minnesota Multiphasic Personality Inventory (MMPI) to identify patient traits associated with poor response to treatment. The authors found a positive correlation ($r = 0.42$; $P < 0.05$) between the scale 1 of the MMPI (Hypochondriasis scale) with the total pain index and headache days. It is not surprising that the study demonstrated a positive correlation between the scale 1 and these indices, as this particular scale assesses for concerns related to somatic complaints and pain. The study also cites other commonly suggested risk factors for relapse or poor treatment response including male gender, chronicity of headache disorder, tension-type or combined headache as the primary headache disorder, use of multiple analgesics, and overreliance on naturopathy or homeopathy [57–59]. Such an effort to identify variables or subgroups within headache sufferers can help clinicians to select appropriate patients for behavioral intervention referral. Future studies to better identify these patient traits would be critical, as the outcomes of behavioral intervention efficacy studies are mixed.

Limitations of Behavioral Interventions

Numerous studies demonstrate the efficacy of behavioral interventions for the management of headaches. In fact, in its 2018 Consensus Statement, the American Headache Society dedicates a section to biobehavioral therapies and cites studies that indicate Grade A evidence for the use of CBT, biofeedback, and relaxation techniques for the prevention of migraine [60]. However, a more recent systematic review has challenged the quality of the studies, which support the use of behavioral interventions for the management of headaches, specifically migraine headaches. In

their 2019 Cochrane Review, Sharpe et al. concluded that existing randomized controlled trials of psychological therapy, including behavioral interventions, for chronic or episode migraine sufferers did not provide good-quality evidence [61]. In other words, the Cochrane review was not able to conclude whether behavioral interventions were effective or harmful in the treatment of migraine.

Sharp et al. suggest that the equivocal result of the Cochrane review could be due to several factors. One is that some of the studies administered behavioral interventions in ways that did not require much interaction, if at all, with a therapist. These modalities included self-directed, home-based, or internet-delivered interventions. The authors suggest that the lack of evidence for these interventions may be due to the way the interventions were implemented and not necessarily the interventions themselves.

Another suggestion by the review authors echoes what was discussed in the previous section of this chapter. Sharp et al. points out that many of these studies do not have enough power to detect patients' traits, which may affect responsiveness to behavioral interventions. Furthermore, many of these studies combine multiple headache types in one study, which may be diluting the effect of these interventions for a specific headache disorder. Lastly, the studies are limited by the difficulty of blinding participants. Studies often use waiting lists or no-treatment groups as control; however, these control groups do not allow for adequate blinding of the participants to the interventions. A better control may be check-ins with a professional for support but without specific behavioral interventions.

In summary, the efficacy of these behavioral interventions for the management of headaches remains controversial. However, the absence of robust evidence for these interventions does not necessarily mean that there is no role for these interventions in clinical settings. Furthermore, it should not prevent clinicians from utilizing the behavioral interventions if they believe them to be appropriate for their patients. The decision to refer patients for behavioral intervention should be made on an individual basis, keeping in mind the variables suggested to be associated with poor treatment response. If patients report limited symptom relief from non-face-to-face behavioral interventions (i.e., self-directed, home-based, or internet-delivered), the clinician should still consider referral to a therapist.

Treatment Approaches: Pharmacological Interventions

While many psychiatric disorders are associated with headaches, most studies on the treatment of psychiatric comorbidities in headache patients focus on depressive disorders and anxiety disorders. The focus on these disorders is not surprising considering the overlap between medications commonly used to treat depression, anxiety, and headaches, especially migraine headaches. Examples of these medications include tricyclic antidepressants (TCAs), serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). Although choosing one

medication to treat both headache and psychiatric illness appears to be the most obvious and logical choice, management is more nuanced and complex [60, 62]. Here are some common considerations.

Monotherapy Versus Polytherapy

In general, physicians aim to use the minimum effective dose of medication for the treatment of any illness. This principle aims to minimize side effects and drug-drug interaction while maximizing the therapeutic benefits of the medication. For example, a physician may choose to prescribe a single medication that can be used to treat both headache and clinical depression, instead of using different medication to treat each condition. An example of this is amitriptyline, a TCA that is used by neurologists for migraine headaches and by psychiatrists for clinical depression. However, monotherapy is not always completely risk-free.

One risk is that monotherapy may result in undertreatment of one of the comorbid disorders. This can happen as a result of a difference between the effective doses of a medication for different illnesses. For example, the recommended dose of amitriptyline for migraine prevention is about half or less than that of the typical dose for the treatment of major depressive disorder [63–65].

However, amitriptyline, like other TCAs, has mainly been replaced in psychiatric practice by SSRIs and SNRIs because they are safer to use with less risk of side effects even on higher doses. Therefore, although treatment of migraine and depression with amitriptyline allows the physician to minimize the total number of medications, patients may experience more side effects on this higher dose monotherapy compared to a polytherapy regimen of an SSRI (for clinical depression) combined with a lower dose of amitriptyline (for migraine prevention).

Similarly, trying to use only one medication to treat headache and comorbid psychiatric disorders may result in the use of non-first line agents [62]. While antiepileptics (divalproex sodium, valproate sodium, topiramate) have level A evidence for migraine prevention, antidepressants such as amitriptyline and venlafaxine have level B evidence rating for migraine prevention [66]. Furthermore, SSRIs and SNRIs lack consistent evidence for the prevention of episodic tension-type headaches [67]. However, antidepressants may be used over the first-line antiepileptics when trying to treat both unipolar depression and migraine, resulting in inadequate treatment of headaches [60, 68]. In reverse, a physician may choose topiramate, an effective medication for migraine headaches but not a first-line agent for bipolar disorder, resulting in inadequate management of bipolar disorder [66]. Thus, polytherapy may allow the physician to use first-line agents for both headache and psychiatric disorders, while monotherapy may not.

Another benefit of using polytherapy for comorbid disorders is that it allows for easier medication adjustments [62]. Both headache and psychiatric disorders can change over time (i.e., symptoms, intensity, frequency), and they do not necessarily

change concurrently. For example, a person may experience worsening of their major depressive disorder, while migraine symptoms remain well controlled. If this patient is already on a high dose of an antidepressant, such as amitriptyline, the next logical step would be to cross-titrate the antidepressant to another agent or add on an adjunctive medication. In the former case, it would be challenging to cross-titrate the medication without risking relapse in migraine headaches. Such a dilemma could be avoided if the patient was taking separate medications for depression and migraine. Of note, the same cases could be made for headache and comorbid anxiety disorders, as the pharmacotherapy of anxiety disorders (i.e., generalized anxiety disorder, panic disorder, obsessive-compulsive disorder) largely overlaps with that of clinical depression.

While this concept of therapeutic independence avoids some of the risks of monotherapy, there are potential issues. As mentioned above, an increased number of medications means an increased risk of side effects and drug-drug interactions. Serotonin syndrome is a rare but potentially serious side effect of increased serotonergic tone, which can result from combining serotonergic medications such as triptans and serotonergic antidepressants (i.e. TCA, SSRI, SNRI). The evidence for increased risk of serotonin syndrome as a result of co-prescribing triptans and serotonergic antidepressants is mixed [69]. A study published in 2018 found that the incidence of serotonin syndrome in patients co-prescribed triptan and SSRI or SNRI was significantly low. In this study, only 7 out of 19,017 patients who were co-prescribed triptan and SSRI or SNRI met the criteria for serotonin syndrome. In other words, the incidence rate in this study was 0.6 cases per 10, 000 person-years (95% CI, 0–1.5) [70]. Based on this, clinicians should not avoid prescribing triptans with serotonergic antidepressants when indicated, but remain mindful of the potential risk, especially when other serotonergic medications are added. Additionally, it should be noted that certain psychiatric medications (i.e., SSRIs, SNRIs, bupropion) can potentially cause headaches as a side effect; conversely, beta-blockers are used for the treatment of migraine headaches and carry the risk of worsening depression, although this remains somewhat controversial [62, 71].

In summary, in the absence of a clear, evidence-based guideline for treating comorbid depression/anxiety and headache disorders, patients may benefit from individualized treatment plans. Physicians should weigh the pros and cons of monotherapy carefully. For example, it may be reasonable to consider treating mild psychiatric disorders with behavioral interventions while treating severe headaches with medication and vice versa. In favor of this, the National Institute for Health and Care Excellence (NICE) in the United Kingdom has published a guideline that recommends CBT and not antidepressants as the first-line treatment for subthreshold or mild clinical depression [72].

Screening for Psychiatric Comorbidities

Due to the complex relationship between headaches and psychiatric comorbidities, a headache specialist needs to be able to recognize psychiatric disorders in headache patients. As mentioned earlier in this chapter, mood and anxiety disorders are common in headache patients, and screening is recommended in all patients [73]. Recognition and treatment of clinical depression and anxiety disorders are essential not only for the patient's mental health but also for the optimization of their headache treatment. Although more studies are required to quantify the effect size of these benefits, treatment of anxiety and/or clinical depression will have a positive impact on overall headache prognosis, response to headache treatment, and adherence to headache treatment. Additionally, screening for substance use disorder could identify patients who are at risk of medication overuse or drug-seeking behavior. Screening for bipolar disorder could prevent misuse of antidepressants for the treatment of headaches, as antidepressant use without concurrent mood stabilizer could precipitate a manic state in bipolar disorder [74].

Previous studies have looked at established screening tools in their effectiveness in screening for psychiatric comorbidities in patients with headache disorders. These include the Patient Health Questionnaire-9 (PHQ-9), Beck Depression Inventory-II (BDI-II), and Generalized Anxiety Disorder-7 (GAD-7) [74]. A recent study on the PHQ-9 and Hospital Anxiety and Depression Scale (HADS) demonstrated that the two screening tools perform similarly in terms of their sensitivity and specificity for detecting a major depressive episode. Using traditional cut-off scores of 10 and 8, respectively, for PHQ-9 and HADS, the former had a sensitivity of 82.0% and specificity of 79.9%, while the HADS demonstrated 86.5% sensitivity and specificity [75]. The authors of this study conclude that the cut-off point for screening can be adjusted depending on the goal of the screening. For example, if the headache specialist has limited means to refer their patients to a mental health provider, then raising the cut-off to increase specificity would be desirable.

Despite the early supporting evidence for screening, headache specialists may hesitate to screen their patients for psychiatric disorders. Reasons for this hesitation include fear of invoking a sense of stigma in their patients, limited time and financial resources to purchase and implement screening tools, limited access to mental health treatment, and the concern for false-positive or false-negative screens without adequate mental health training to confirm the result with clinical assessment [76]. Therefore, until definitive guidelines are established, the decision to screen and refer patients to mental health treatment is contingent on the headache specialist's comfort level with psychiatric disorders as well as their ability to provide referrals to appropriate mental health care.

Conclusion

The association between headache and psychiatric disorders is undeniable. It is inevitable that while treating patients with headache, one will also encounter psychiatric illnesses, especially mood and anxiety disorders. Until an evidence-based guideline is established for the management of these patients, physicians must use their clinical judgment with regard to screening for psychiatric disorders, referring to mental health treatment and coordinating with mental health providers to devise a treatment plan optimized for individual patients. Collaborative approach for the treatment of headache and comorbid psychiatric disorders is crucial in creating a treatment plan that minimizes adverse effects but effectively treats both the neurologic and psychiatric disorders. These treatment plans can include a combination of pharmacotherapy and behavioral interventions depending on the patient's need and underlying traits.

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Chapter 9
Nutraceuticals

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Introduction

While our current medical practices rely heavily on pharmaceuticals, many patients are interested in alternative treatment options, such as nutraceuticals. Parents of young children, for example, often prefer nutraceuticals in the hopes of them being safer or without any side effects. One study in 2014 surveyed a collection of 124 children in Italy and found that 76% of these patients used complementary and alternative medicine (CAM) [1]. Therefore, clinicians need to be informed about the efficacy and safety of alternative therapies. This chapter will provide an evidence-based assessment of the most common nutraceuticals used for headache. Please note that the 2012 American Academy of Neurology (AAN) guideline "Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults" was retired in 2015 after safety concerns for butterbur. The AAN no longer supports these recommendations and is in the process of updating guidelines as of print time [2].

Magnesium

Magnesium is a micromineral used for migraine management in both intravenous and oral forms. It works by blocking the calcium channel in the NMDA receptor, therefore preventing glutaminergic excitatory activity. Magnesium is also essential for mitochondrial functioning as it lowers membrane permeability and reduces the possibility of spontaneous neuronal depression due to hyperexcitability [3]. Low

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levels of magnesium are found in serum, saliva, cerebrospinal fluid, and specific areas of the brain on MR Spectroscopy in those with migraine [3]. Patients with cluster headaches and migraine, especially menstrual migraine, have low levels of magnesium [4].

Dietary surveys reveal that consumption of magnesium in Europe and the United States (US) is low and, in the US, consumption has been declining over the last 100 years. According to the National Health and Nutrition Examination Survey (NHANES) of 2005–6, nearly half of American adults have inadequate intake [4]. Signs and symptoms of low magnesium in the nervous system may include migraine, depression, nervousness, nystagmus, paraesthesias, poor memory, seizures, tremor, and vertigo [4].

Magnesium supplementation theoretically inhibits hyperexcitability and cortical spreading depression, a process that may lead to migraine and aura [3]. Studies find low magnesium levels in serum, cerebrospinal fluid, saliva, and brain tissue (via ^{31} phosphorus-magnetic resonance spectroscopy) [5]. In vitro animal and human studies show low magnesium can lead to cerebral arterial vasospasm by potentiating the contractile response of blood vessels to vasoactive substances like serotonin. Low magnesium in the cortex can also enhance the sensitivity of NMDA receptors to glutamate, leading to epileptiform discharges and cortical spreading depression. Lastly, magnesium may be proinflammatory via mechanisms involving platelet aggregation and serotonin release [6].

Magnesium and its effects on migraine treatment and prevention has undergone evaluation in placebo-controlled studies. A meta-analysis of randomized controlled studies by Choi and Parmer between 2000 and 2005 did not find strong evidence for magnesium treatment [3]. A double-blind placebo-controlled trial by Pfaffenrath in 1996 did not see benefit from the prophylactic use of 486 mg of magnesium in the form of granulates dissolved in a glass water after 12 weeks of treatment; however, study patients had already failed beta-blockers and peripheral vasodilators. Therefore, these patients may have been nonresponders in general, and it is difficult to generalize these results to the average patient with migraine [5]. More promising data for magnesium emerged in a 1996 study by Peikert. This study found that magnesium was beneficial for headache in the first 5–8 weeks of treatment in 68 of 81 participants. After 9 to 12 weeks of 600 mg of magnesium consumption, there was a reduction in headache frequency by 41.6% (compared to 15.8% in placebo) [6]. Another meta-analysis completed by Chiu in 2016 reviewed a more significant number of clinical trials evaluating the intravenous (IV) use of magnesium during an attack and the oral use of magnesium to prevent attacks. The conclusion was that IV magnesium resulted in significant relief across time intervals (15–45 min, 120 min, and 24 hours) after administration. Oral magnesium treatment significantly reduced migraine frequency and attack severity [7]. The above data allowed magnesium to be assigned level C evidence, meaning that it may be effective for the treatment of migraine [3, 7].

Data regarding the use of magnesium in the pediatric population is limited. Two studies showed positive findings. One randomized, double-blinded, placebo-controlled trial tested oral magnesium versus placebo for 16 weeks. The magnesium

group had fewer headaches, with reported decreased severity in pain ($p = 0.0037$ and $p = 0.0029$, respectively) [8]. A second non-blinded study provided magnesium to 45 children with improvement in Migraine Disability Assessment (MIDAS) scores, headache days, and use of analgesics. Magnesium oxide was given at a dose of 9 mg/kg/day, divided three times daily with food, and 2.25 g of magnesium pidolate twice daily, respectively [9, 10].

Magnesium supplementation is widely considered benign. Side effects are limited and may include flushing, diarrhea, loose stools, or gastrointestinal discomfort [11]. For this reason, many providers have touted magnesium as a safe treatment option. However, recent studies are questioning magnesium and its safety in fetal bone development. As a result, the FDA reclassified magnesium sulfate injections during pregnancy as category D in 2013 (downgraded from category A) [9, 11]. As of publication time, the authors recommend avoiding magnesium use in pregnant patients until there is more definitive research.

The AAN gives magnesium citrate oral supplement a level B evidence rating when given at a dose of 400 to 600 mg daily for migraine prevention [3]. For the acute treatment of migraine aura, there is Level B evidence for 1–2 g of IV magnesium per the 2015 American Headache Society (AHS) Evidence Assessment and the AAN [11].

Riboflavin (Vitamin B2)

Riboflavin is another supplement heralded as a migraine treatment for many years. Also known as vitamin B2, it is a water-soluble vitamin that functions as a cofactor in the mitochondrial electron transport chain (working in energy metabolism and generation). It is a precursor to flavin mononucleotide and flavin adenine dinucleotide [12]. Discussion of its potential use in migraine was born in the clinical outcomes of supplementation for those with mitochondrial myopathies and in the theory that impaired oxygen metabolism may contribute to migraine [12, 13]. The theoretical role it may play in migraine is in its effect of cortical spreading depression and decreased migraine threshold. These may both result from reduced ATP production and energy metabolism and increased neuronal information processing [9, 12].

Conflicting data exists regarding riboflavin and its benefit in migraine prophylaxis. Diener and colleagues demonstrated that riboflavin supplementation might be an acceptable prophylactic option. Boenke and colleagues completed an open-label study amongst tertiary care centers to determine the effect of riboflavin. After 3 months of treatment, headache attack frequency decreased from four per month to two per month in those receiving riboflavin ($P < 0.001$). Headache attack frequency and the use of abortive agents (triptans, but not other analgesics) were both reduced at 3 months and 6 months post-treatment, compared to placebo. There was no change in headache intensity in the treatment group [12]. This finding is supported by data from a study by Sandor, which investigated the effect of prophylactic

beta-blockers and riboflavin on auditory-evoked cortical potentials. In those treated with riboflavin, there was a reduction in headache attacks from 3.51 attacks/month to 1.7 attacks/month [14].

There is limited data available for riboflavin in pediatric patients. A double-blind crossover randomized-controlled trial (RCT) found no benefit in a small group of children when given at a dose of 50 mg per day [15]. Further research is needed.

Side effects of riboflavin and medication interactions with this vitamin appear limited. Amongst those in Boenke's study, one patient withdrew due to gastrointestinal intolerance, deemed a result of daily aspirin use [12]. Though harmless, riboflavin can cause a bright yellow discoloration of urine [13]. It may cause diarrhea and polyuria, as well [11].

Riboflavin has Level B evidence for migraine prevention in adults according to the AAN. The recommended dose is 400 mg daily [11].

Butterbur

Butterbur is a group of herbaceous perennial plants with a long history of use in alternative medicine. Its two major components are petasin and isopetasin, which exert anti-migraine effects [16]. It is administered in standardized amounts of petasin/isopetasin (minimum 15%, corresponding to 7.5 mg) due to the instability of petasin, which spontaneously converts to isopetasin [16].

Petasin and isopetasin may work to alleviate migraine by inhibiting leukotriene synthesis in leukocytes and by inhibiting voltage-gated calcium channels of arterial smooth muscle cells [16]. Another theory is that isopetasin may lead to TRPA-1-dependent desensitization of nociceptors that lead to neurogenic inflammation [16]. TRPA-1 is a cation channel expressed by primary sensory neurons.

A double-blinded, randomized, placebo-controlled, parallel-group study was conducted in Germany evaluating the use of butterbur in headache treatment [17]. Responders (the number of participants who achieved a reduction in headache frequency by 50%) were 45% in the treatment group versus 15% in the placebo group. The duration and intensity of headaches also were reduced by the administration of butterbur. Additionally, there was a reduction in acute migraine medication use in the study group [17]. These changes appeared after 3 months of daily butterbur use. In a study by Lipton, researchers compared a branded butterbur extract (Petasites) at doses of 50 mg twice daily and 75 mg twice daily versus placebo. Those treated with 75 mg of Petasites extract had a 45% reduction in the number of attacks over 4 weeks compared to 28% in the placebo group ($p = 0.005$). It was more effective than the 50 mg dose ($p = 0.04$). In comparison to placebo, there were a more significant number of patients with a 50% reduction in headache frequency. There did not appear to be an effect on headache attack duration or intensity [18].

Butterbur has been studied in pediatric patients, as well. In one multicenter prospective open-label study conducted by Pothmann, 108 children between six and 17 years of age were treated with 50 to 150 mg of butterbur root extract. Children

aged 6–9 years and 10–17 years experienced a decrease in headache frequency from 9.4 to 4.0 and 9.7 to 5.8, respectively, after 4 months of treatment. There were 77.2% responders in all those sampled, with responders defined as participants who achieved a reduction of at least 50% in monthly migraine attack frequency. Attack duration and severity appeared reduced as well [19]. Of note, much of this data is based on patient diary entry and may be subjective. Further placebo-controlled trials of butterbur are needed.

While it may be effective, Butterbur is not safe. Patient complaints are largely gastrointestinal-related [19]. In Pothmann's study, four patients reported mild eructation [19]. There was also a dose-dependent effect on burping for those in the Lipton study [18]. A study by Diener reported slight elevations in ALT, AST, bilirubin, and erythrocyte count. However, it did not find clinical correlates to the changes above normal ranges [17]. Butterbur, when not purified, contains pyrrolizidine alkaloids, which are carcinogenic. Pyrrolizidine alkaloids can cause liver damage (manifested by elevated liver enzymes, jaundice) and liver cancer. These alkaloids need removal via high-pressure liquid carbon dioxide extraction [19].

There is currently no level of evidence provided by the AAN for butterbur administration in migraine. The previously recommended dose was 75 mg twice daily. While it is considered effective, the Academy retired its recommendation for butterbur in July 2012 (previously Level A evidence). The US does not regulate herbal products and thus cannot assure that the US-derived formulations are adequately purified. Petadolex® is a reportedly purified version, but may not be produced and/or available as of publication time [20].

Coenzyme Q10

Coenzyme Q10 (CoQ10) is a naturally occurring, hydrophobic substance in all cell membranes that is critical to the electron transport chain and the function of the mitochondria. It transfers electrons from the NADPH dehydrogenase complex and the succinate-Q-reductase complex to Cytochrome C, thereby helping to create energy. Additionally, CoQ10 functions as an antioxidant, an anti-inflammatory, and a protectant of myocardium from post-ischemic reperfusion injury [9, 21].

The role of CoQ10 with regard to headache pathophysiology is not entirely understood. Magnetic resonance spectroscopy (MRS) studies and DNA analysis in some migraine patients suggest mitochondrial dysfunction may result in migraine [21]. Others have noted the depletion of CoQ10 during the inflammatory component of migraine [9].

In an open-label, parallel, add-on, match-controlled trial, 80 patients with migraine showed improvement with CoQ10 compared to control. The control group included patients who continued taking their current preventive medications, and the treatment group included participants on a preventive medicine (a combination of a tricyclic antidepressant and sodium valproate) plus 100 mg Coq10 daily. Mean attack frequency decreased by 1.6 in the CoQ10 group versus 0.5 in the control

group ($p < 0.001$). The mean decrease in headache severity (assessed via Visual Analogue Scale (VAS)) was 2.3 vs. 0.6 ($p < 0.001$) in the CoQ10 and control groups, respectively. There was also a significant reduction in associated headache symptoms, such as nausea, photophobia, and phonophobia [22]. In another study published in Cephalalgia, researchers supplemented CoQ10 in patients who were not on preventive therapy. These patients were classified as episodic migraine with or without aura and had two to eight headache days per month at baseline. Thirty-one of 32 patients completed the study (one patient was lost to follow up). There was a 50% reduction in the number of migraine headache days in 61.3% and a 25% reduction in headache days in 93.5% of participants. Mean migraine attack frequency decreased from 4.85 to 2.81 ($p < 0.001$) in the treatment group. There was no statistically significant benefit found with regard to the severity of headache reported by participants. These patients experienced benefits as early as the first month of treatment with more substantial improvement at 3 months [21].

A 2011 random, crossover, double-blind, placebo-controlled study investigated CoQ10 in children and adolescent patients. Participants received either 100 mg CoQ10 chewable tablet or a placebo chewable tablet. There was no statistically significant difference in headache frequency or severity between the treatment group and the placebo group [23].

Supplementation of CoQ10 is generally well tolerated. The studies included above report little to no side effects. However, there is the potential of anorexia, dyspepsia, nausea, diarrhea, and rash [11]. Some experts suggest testing levels of CoQ10 before supplementation, as there are reports of deficiency in patients aged 3–22 with migraine (with and without aura), chronic migraine, and probable migraine [24].

The AAN and AHS give CoQ10 Level C evidence when administered at a dose of 100 mg three times daily [9, 11].

Melatonin

Melatonin is a hormone that regulates sleep. Light projected via the retinal ganglion cells stimulates the suprachiasmatic nucleus (located in the hypothalamus) to regulate melatonin release from the pineal gland [25]. Light inhibits the release of melatonin, and darkness promotes it [26]. There is a solid relationship between sleep and migraine. Many with migraine report a history of sleep disturbances during infancy; this suggests a genetic link between headache and sleep disorders [27]. Many patients with migraine also report the resolution of their migraines with sleep [26]. Migraine patients have been found to have low levels of a metabolite of melatonin, 6-sulphatoxymelatonin [25].

Melatonin may work through various pathways to prevent and treat migraine. It may protect the brain from damage and maintain its structure and function by acting as a membrane-stabilizing factor [25]. It can inhibit nitric oxide synthesis, dopamine release, glutamate-induced excitotoxicity, and calcitonin gene-related peptide

(CGRP) release [25]. Additionally, melatonin itself may provide pain relief. Melatonin shares its structure with indomethacin, likely inhibiting prostaglandins, and other pain substances [25, 26]. Melatonin has also been touted as having anxiolytic and anti-depressant properties [25].

A pilot study led by Bougea investigated the use of 4 mg of melatonin 30 minutes before bedtime for 6 months in 49 patients with chronic migraine and chronic tension-type headache. Thirty-seven of the participants met the criteria for migraine. After 6 months, the patients with migraine had experienced a decrease in attack frequency, from 4.72 per month to 2.1 per month ($p < 0.001$) [28]. Scores on the HIT-6, which is a self-administered six-item questionnaire measuring headache impact, decreased from 63.51 (max score 78) to 44.37 ($p < 0.001$) [28]. Long and colleagues completed a systematic review, which included seven studies conducted between 1998 and 2018. Overall, melatonin was found to be effective at reducing headache frequency, duration, and intensity. Of note, the efficacy of prophylactic melatonin varied between studies. Doses ranged from 2 mg to 4 mg, and duration of use was between 2 and 6 months (1 study included 25/50 mg of Agomelatine, a melatonergic agonist and atypical antidepressant) [25].

Melatonin has been studied for other headache types aside from migraine. Gelfand and Goadsby published a 2016 review of melatonin in headache syndromes. They reference randomized placebo-controlled studies as well as case reports of melatonin in cluster headache (doses ranging from 5–10 mg nightly). In the controlled trial (which unfortunately only had a few patients), melatonin was started around the second to the tenth day of a cluster cycle and was superior to placebo at decreasing cluster attack frequency within 3 days of initiation [26]. Rozen published three cases of melatonin-responsive hemicrania continua (likely due to its structural similarity to indomethacin) in *Headache*. These patients were previously unresponsive or unable to taper off of daily indomethacin but saw significant reductions in headache frequency when given melatonin in doses ranging from 9 mg to 15 mg every evening. The data suggests that patients should begin 3 mg of melatonin nightly with a dose increase of 3 mg every three to five nights (maximum dose of 24 mg). Patients on indomethacin should start to taper their dose of indomethacin by 25 mg every 5 days once they begin to achieve headache improvement on melatonin [29]. There is also a case report of long-lasting autonomic symptoms with hemicrania (LASH) syndrome responsive to 10 mg of melatonin. This patient achieved headache freedom at six-month follow-up on nightly doses of melatonin, no longer requiring indomethacin [30].

Melatonin can be effective in children. Miano and colleagues completed an open-label trial of melatonin in children with primary headaches. A total of 22 children enrolled in the trial. Headache types included migraine with and without aura and tension-type headache. Participants in this trial experienced a 50% reduction in headache attack frequency when taking 3 mg of melatonin at bedtime [31]. In a second study, 60 children with migraine were given 0.3 mg/kg melatonin for 3 months with positive outcomes, including a reduction in monthly frequency, severity, and duration of headache [32]. A double-blind, placebo-controlled trial was started in 2014 by Barlow in children with post-concussive syndrome following

mild traumatic brain injury. Ninety-nine children ranging in age from 13 to 18 years who were symptomatic (headache, mood disturbances, or learning disability) at 30 days post-injury were assigned to sublingual doses of melatonin (3 mg or 10 mg versus placebo). This trial was expected to conclude in November of 2019; however, results were not available as of press time. It is postulated that melatonin can help to decrease posttraumatic headache and improve post-traumatic sleep disturbances due to its action on the GABAergic system [33].

Melatonin is very safe and has minimal side effects. It has been given to people at doses of 20 to 100 mg orally, and at 10 mg/kg IV to neonates with no apparent toxicity other than transient drowsiness [26]. Nocturnal asthma has been noted in some with elevated melatonin levels [26]. In a systematic review by Long and colleagues, five of the articles reported a total of 33 adverse events. Side effects included sleepiness, fatigue, increased libido, dizziness, hypotension, epigastralgia, nervousness, nightmares, pruritus, dry mouth, constipation, and alopecia [25, 32]. There have been reports of increased enuresis, diarrhea, rash, and hypothermia (induced by 3 mg melatonin in the elderly). There is limited information regarding melatonin use during pregnancy. It is metabolized by CYP1A2 and CYP2C19; therefore, the dose may need to be altered in patients also taking CYP1A2 inhibitors. For example, tricyclic antidepressants, fluvoxamine, and cimetidine may increase melatonin levels [27]. Providers should also be mindful of patients on medical therapy for diabetes and hypertension, as melatonin may decrease blood pressure and serum glucose [27].

There is currently no grade level provided by the AAN for melatonin administration in migraine. Providers may recommend 2 mg to 10 mg every evening. Patients may need to adjust their dose to avoid residual drowsiness in the morning. For optimum efficacy, patients should avoid or significantly limit exposure to lights (especially blue light) after taking melatonin.

Feverfew

Feverfew (Tanecetum parthenium) is a perennial herb belonging to the *Asteraceae* (daisy) family. It is native to Asia Minor and the Balkans, but is now grown worldwide [34]. The dried leaves have been used in medicine for many years, but its extract is now used by some to prevent migraine and relieve associated migraine symptoms [34].

The anti-migraine properties of feverfew may come from a component called parthenolide, a sesquiterpene lactone [34]. However, the mechanism of action is not fully understood. The parthenolides, found in the leaves, are believed to inhibit prostaglandins, which play a role in the contractile and relaxant mechanisms of blood vessels, and may inhibit serotonin secretion [9, 34]. Chrysanthenyl acetate is an essential oil component of feverfew. This oil constituent may inhibit prostaglandin release and provide analgesic effects, as well [34]. Feverfew may also inhibit nitric oxide synthesis, nuclear factor-kappaB (a transcription factor in

pro-inflammatory cytokine signaling), and calcitonin gene-related peptide (via inducing nociceptor desensitization through targeting transient receptor potential ankyrin 1) [35]. A final alternative theory links melatonin found within feverfew to its anti-migraine properties [34].

A Cochrane Database review found 11 double-blinded RCTs of feverfew use, of which 6 were ultimately reviewed [36]. The studies assessed the use of self-administered oral capsules of feverfew given one to three times daily over 2–8 months. Studies differed in dosage and type of feverfew administered and included dried, powdered feverfew extract, alcoholic feverfew extract, and carbon dioxide extract. The results vary amongst studies, but the overall conclusion is that feverfew may reduce migraine attack frequency by 0.6 per month compared to placebo [36]. Only one study, Palevitch 1997, showed improvements in the intensity of migraine attacks when treated with feverfew. Otherwise, no studies found statistically significant improvements in this measured outcome. Three studies reported a decreased incidence in the occurrence of nausea and vomiting (Johnson 1985, Murphy 1998 and Palevitch 1997) [36]. A 2011 study by Cady was excluded as participants used a combination of feverfew and ginger as an abortive. The results of this study, though, showed that there was pain relief (or only mild headache) at 2 hours in 63% of the treatment group versus 39% in placebo ($P = 0.002$). The recurrence rate for those who achieved pain-freedom was 20.4% within 22 hours [36].

A 2019 multicenter, prospective, observational study examined children and adolescents with migraine taking feverfew (150 mg) as a component of a nutraceutical supplement called Partena®. This supplement also included magnesium (169 mg), riboflavin (4.8 mg), Coq10 (20 mg), and Andrographis paniculata (100 mg). Among 91 patients, 55% of the migraine without aura group and 85% of the migraine with aura group had a reduction of attack frequency at 16 weeks. The migraine without aura group had a reduction during treatment, but the migraine with aura group did not achieve this reduction until the end of the 16-week study period. Patients also reported a decrease in the intensity of their headaches [35].

Feverfew is considered relatively safe. There is no known increased risk of cancers with long-term use. Mouth ulceration, dermatitis, and gastrointestinal symptoms have occurred in users [34], which may be a result of the formulation of feverfew used [34]. Those given a combination nutraceutical pill (Partena®) reported nausea and diarrhea [35]. The study by Johnson in 1985 also reported that two of the participants who had complete resolution of migraine during the treatment arm had a recurrence of incapacitating migraine after abrupt discontinuation. Post-feverfew discontinuation syndrome, as it is called, can include nervousness, tension, headaches, insomnia, stiffness, joint pain, and tiredness [37]. Feverfew is contraindicated in those allergic to other families of the *Asteraceae* species (chamomile, ragweed, or yarrow). Those on anticoagulants should avoid feverfew due to its ability to inhibit platelets [37]. It should also be used with caution in women of childbearing age as it may stimulate uterine contractions during pregnancy [9].

There is no recommendation for feverfew in the Practice Guideline Update Summary for Treatment of Migraine in Children and Adolescents by the AAN and the AHS. The AAN Headache Quality Measurement set of 2014 gave Feverfew

50–300 mg twice daily or 2.08–18.75 mg three times a day for the MIG-99 preparation level B evidence in its list of drugs recommended for use in migraine prophylaxis.

Vitamin D

Vitamin D is a crucial vitamin implicated in many neurologic conditions, including migraine. Low levels may be related to latitude and decreased exposure to sun. Low vitamin D levels and vitamin D receptor polymorphisms are linked to a higher prevalence of headache and migraine [38]. A study of 2601 Finnish men from the Kuopio Ischaemic Heart Disease Risk Factor found that those in the lowest serum 25-hydroxyvitamin D quartile had 116% higher odds of developing or experiencing frequent headache [38].

The active metabolite of vitamin D is $1,25(OH)_2D$. It is involved in transcription, which could result in "protective genes" like anti-inflammatory cytokine IL-10 or suppression of those that promote pain and inflammation (i.e. IL-1 beta) [38]. Vitamin D supplementation may decrease factors such as C-reactive protein [39]. The vitamin D receptor and metabolizing enzymes are expressed in nociceptive sensory neurons, as well [38].

Studies regarding headache frequency and low serum vitamin D levels are available, but data investigating the effects of supplementation is limited. A randomized, double-blind, placebo-controlled trial was completed with 65 migraine patients aged 10–61 years. The mean headache attack frequency per month was seven in the control group compared to 5.9 in the intervention group receiving weekly 50,000 IU of vitamin D. However, the mean difference in headache frequency between each group was not statistically significant ($P = 0.06$) [39]. A randomized, double-blind placebo-controlled, parallel-arm study investigated supplementation of 20 mg simvastatin daily with twice daily 1,000 IU vitamin D3 versus placebo. Participants maintained their headache abortive and prophylactic medications, but were asked to keep intake regimented. The study ran for 36 weeks, with 52 of the 57 applicants achieving full completion (100% completion at 24 weeks). The treatment group had a more significant decrease in the number of migraine days; there was a change of −8 days in the treatment group at weeks one through 11 compared to +1 days in the placebo group. The difference in the number of days participants used abortive medications during weeks one to 12 was 4.5 fewer days in the treatment group, and 1.0 fewer days in the placebo group ($p < 0.002$). The benefit appeared to remain during weeks 13 through 24; there were seven fewer days of acute medication treatment in the treatment group compared to two fewer in the placebo group ($p < 0.001$) [40].

Pediatric studies regarding vitamin D and migraine are even more limited. One retrospective study evaluated children for vitamin D insufficiency and deficiency. Migraine frequency, duration, and pediatric MIDAS scores were higher in the insufficiency group (levels between 10 and 20 ng/mL) compared to the deficient group

(<10 ng/mL). Children who were vitamin D insufficient received vitamin D supplementation (2,000 IU per day for 2 months, followed by 600 to 1,000 IU daily maintenance for 6 months). Migraine frequency and duration were significantly decreased in the treated group [41]. In another study, Cayir and colleagues supplemented vitamin D in children simultaneously on amitriptyline for migraine prevention. This study showed a statistically significant decrease in attack frequency in the participants [42].

Most studies did not report adverse events or side effects with vitamin D supplementation. The study investigating vitamin D and simvastatin reported abdominal discomfort in those receiving placebo only. There were reports of myalgias and skin rash in both groups. The results may be obscured by simvastatin use, which may cause both of these symptoms. However, excess vitamin D could cause hypercalcemia, which can lead to gastrointestinal upset, weakness, and polyuria, among other symptoms [40].

There are no guidelines for supplementation of vitamin D or its concomitant use with simvastatin. Based on risk factors, providers may discuss with patients the utility of checking a vitamin D level. If a patient is vitamin D insufficient or deficient, there appears to be little risk to supplementation. The evidence for benefit for migraine, however, is not robust, and further research is needed. In terms of simvastatin, many patients find it difficult to tolerate due to myalgias (though mainly seen at higher doses), which may limit its use.

Vitamin E

Vitamin E is explicitly used for the prevention of menstrual migraine. Many women with migraine (60%) report an association between their migraines and their menstrual cycle [43]. These migraines tend to be more severe and medically refractory. Mini-prophylaxis with NSAIDs or triptans during menses is often utilized but runs the risk of medication overuse. Therefore, vitamin E is offered as a safer alternative [43].

Vitamin E inhibits prostaglandins in the body. During the follicular and luteal phases, there is a threefold-increase in prostaglandins in the endometrium. Prophylactic use of vitamin E may inhibit this prostaglandin production and provide headache benefit [43]. In rat headache models, vitamin E is protective to the brain. Vitamin E inhibits free radical production, regulates calcium dependent processes, and supports the antioxidant redox system [44].

Ziaei and colleagues published a placebo-controlled double-blinded study in 2009. They evaluated women between 20 and 30 years old with regular menstrual cycles and no consumption of exogenous hormones or other preventive medications in the 3 months prior. Sixty-seven qualifying women completed the study, and they were given 400 IU of vitamin E daily for 5 days, from 2 days before to 3 days after the onset of menstruation. The treatment and placebo group both had reductions in migraine severity, disability, and use of abortive medications (ibuprofen). The

magnitude of the reduction was statistically more significant in the treatment group compared to placebo, and the participants taking vitamin E reported more considerable improvement in photophobia, phonophobia, and nausea [43].

The above-mentioned study did not note side effects among those receiving vitamin E supplementation. One publication reported a theoretical risk of decreasing corticosteroid and cyclosporine efficacy in those with comorbid autoimmune disease. Vitamin E may also contain L-canavanine which has been reported to cause a lupus-like autoimmune disease, as well [37]. It should also be noted that vitamin E inhibits activation of vitamin K-dependent clotting factors and platelet aggregation. Very low levels may cause increase in ischemic disease, while very high levels may increase hemorrhage risk [45].

There are no guidelines supporting vitamin E supplementation for migraine prevention. However, providers may consider recommending vitamin E supplemented at 400 IU daily for 5 days during menstruation or throughout the month (for those who may have difficulty remembering or tracking their menstrual cycle) with little risk.

Boswellia serrata

Boswellia serrata (Sallaki H15) extracts are mentioned in patient-based blogs for their effect on headache and migraine. There are gum-resin extracts derived from Boswellia, which have been used for centuries in medicine. Boswellia contains monoterpenes, diterpenes, triterpenes, tetracyclic triterpenic acids, and four pentacyclic triterpenic acids that inhibit pro-inflammatory enzymes and have analgesic properties [46, 47]. Another name for the extracts is Indian Frankincense. In the Italian cohort study of pediatric headache patients, 64% used herbal remedies such as *Boswellia serrata* [1].

Boswellia serrata's function and mechanism of action are poorly understood. In vitro studies have led to multiple proposals. Boswellia has been found to inhibit 5-lipoxygenase (5-LO), leukotriene biosynthesis (i.e. leukotriene B4 (LTB-4)), and human leukocyte elastase [46, 47]. Another study cited by Siddiqui believes that boswellia inhibits tumor necrosis factor-alpha, interleukin-1 beta, nitric oxide, and mitogen-activated protein kinases. Its interactions with proinflammatory cytokines may be a factor in headache management [46].

There are no controlled studies of Boswellia for migraine or other headache subtypes. There was one open-label study of four patients with chronic cluster headache given *Boswellia serrata*. The starting dosage was 350 mg, three times daily, and was increased to as high as 700 mg, three times daily in two patients. All four patients had improvement of headache, which appeared dose-dependent. One patient had a resurgence of symptoms when tapered off due to lack of supply. Otherwise, Boswellia remained in effect for an average of 15 months for three of the patients [47].

Gliacin completed an open-label, prospective, crossover study comparing the effects of indomethacin and Gliacin (a derivative of *Boswellia serrata* extract) in

indomethacin-responsive headaches [48]. There were 27 patients with confirmed indomethacin-responsive headache subtypes included in the study (hemicrania continua, paroxysmal hemicranias, primary stabbing headache, primary cough headache, primary exertional headache, primary headache associated with sexual activity, and hypnic headache). Twenty-one of the 27 patients were considered responders to Gliacin (those who had more than 70% improvement in both headache severity and frequency). Starting dosage for these patients was 250 mg three times a day with unspecified dose increases. The participants' headaches were measured before the trial while taking indomethacin, and while taking Gliacin. The researchers reported that 67% of subjects were more satisfied with Gliacin compared to indomethacin and had fewer side effects. A large caveat to this study is that it was completed by a clinical advisor for Glia Sciences, the manufacturer of Gliacin [48]. Side effects listed by the Gliacin study include abdominal pain, diarrhea, indigestion, lightheadedness, psychiatric, and "any type," which they do not define [48]. There is no safety data supporting its usage in children, pregnant or nursing women, or those with liver or kidney disease.

There is no level of evidence guideline regarding treatment with Boswellia for migraine or other headache subtypes. The aforementioned open-label study by Lampl claims to provide Class IV evidence that oral *Boswellia serrata* reduces the intensity and frequency of headaches in chronic cluster patients [47]. For those considering the use for patients, general recommendations are 300–500 mg given two to three times daily.

Aromatherapy/Essential Oils

Aromatherapy has a long history of use in pain and migraine treatment, but with very little data, understanding, or dedicated rigorous research. Essential oils are applied via the skin or utilized through the sense of smell, and derived from plants [49].

More than 40 plant derivatives are used for medical therapies; but lavender, peppermint, eucalyptus, chamomile, and rosemary are the most accepted [49]. Some postulate that a long-term cooling effect is activated by cold fibers in the skin and results in reduced pain transmission in C fibers. Skin blood flow may increase from peppermint oils mixed with menthol. Finally, the combination of external stimuli and peripheral anesthetic may create "peripheral conditioning of the brainstem reflex." Essential oils influence the central serotoninergic system and increase performance-related activity while decreasing emotional irritability [50].

In randomized, double-blinded placebo-controlled studies, patients with migraine placed lavender or rose oil on the forehead and temple. Assessment of headaches via the visual analogue scale (VAS) took place over 2 hours. There was a greater mean reduction of headache, shorter interval to treatment time, and less spread of headache in lavender users. Lavender also had benefit in migraine prevention. There was no statistically significant benefit to rose oil [51, 52]. Another randomized, single-blinded placebo study had patients with migraine place lavender oil onto the upper

lip and then inhale the vapor for 15 minutes. Through assessment with VAS, there was a more significant mean reduction in headache severity compared to placebo, and lavender was deemed useful in the treatment of symptoms associated with migraine [53]. One abstract assessed groups of people with tension-type headache who used tiger balm, topical placebo, or paracetamol. Headache severity was measured by self-report, and there was a statistically significant difference between the tiger balm group and placebo, but not paracetamol [54].

There are few side effects associated with essential oils. Allergies to components of the oils or sensitivity to smells limit the use of oils in some patients, especially patients with osmophobia as a component of their migraines. Patients may also experience skin irritation when using essential oils [51]. There have been reported cases of prepubertal gynecomastia in repeated exposure to lavender oil [53].

There are no guidelines for the use of essential oils in migraine treatment. Additional studies are required to determine efficacy and tolerability in practice. However, due to its low side effect profile, it may be considered as an abortive agent or supplement to preventive care in migraine patients interested in alternative therapy.

L- 5-Hydroxytryptophan

Serotonin (5-hydroxytryptamine, 5-HT) appears to be involved in the migraine pathway with benefits seen in patients given L-Tryptophan [55]. Urine studies have found that there is an increase in the excretion of 5-hydroxyindoleacetic acid (5-HIAA), the primary metabolite of 5-HT during migraine attacks. This coincides with the rapid decrease of plasma serotonin (5-HT) levels found during migraine attacks [56].

An old study completed at Montefiore Hospital Headache Clinic and published in 1960 followed patients who were given reserpine to induce headaches and then subsequently given serotonin, 5-hydroxytryptamine (5-HT) and a serotonin precursor, 5-hydroxytryptophane (5-HTP). HT and 5-HTP were beneficial in reducing headaches in those with spontaneous, as well as the reserpine-induced, migraine [57]. While we are able to treat individual migraines with selective 5-HT receptor agonists (5-HT 1B/1D/1F), there is still no consensus on serotonin and migraine, as case reports have shown both an increase and decrease in plasma levels during attacks [56].

Ribeiro conducted a parallel, randomized, double-blind trial of 78 patients with chronic tension-type headache treated with 300 mg daily L-5-Hydroxytryptophan (L-5-HTP), another serotonin precursor, versus placebo. Patients followed for 8 weeks showed no statistical change in the number of headache days. However, when assessed 2 weeks after treatment, there was a decrease in the number of days with headache [58]. Sanducci and colleagues then conducted a double-blind placebo crossover study of 21 children aged 6–12 years with migraine. The mean daily dose of 5 mg/kg of L-5-HTP was distributed into three dosages and administered

after meals. The placebo and L-5-HTP groups both had a statistically significant decrease in the frequency of attacks and migraine index, which was calculated by researchers using numerical representations of the frequency and severity of attacks [59]. 5-HTP, at a dose of 600 mg daily, has also been compared with methysergide 3 mg daily in migraine prophylaxis, with each producing similar study results. There was an improvement in 75% of patients taking methysergide versus 71% taking 5-HTP, and this improvement was quantified as a reduction greater than 50% in frequency of attacks or the number of severe headaches. The 5-HTP group noted improvement more so related to the intensity and duration of an attack, rather than a change in the frequency of attacks [60].

No side effects were experienced by any of the children in the Santucci trial [59]. However, there were reports of epigastric pain, urticaria, allergy, diarrhea, and transient insomnia in the trial by Ribeiro. There were no reported changes in weight or blood pressure in those treated by Ribeiro, but others have seen weight gain using 5-HTP, and there has been one case of amenorrhea [58, 60].

There are no guidelines regarding the use of serotonin and its derivatives for headache or migraine.

Vitamin B12/Folate

There has been much discussion in the literature regarding the role of vitamin B12 and folate supplementation in the prevention or treatment of migraine, primarily migraine with aura. The pathophysiology of vitamin B12 utility in migraine prevention may be related to the nitric oxide pathway; vitamin B12 (hydroxocobalamin) has been shown to scavenge nitric oxide species, and nitric oxide is involved in migraine pathophysiology [61].

A second proposed theory involves the vitamin B12/folate pathway and homocysteine. The enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) is an enzyme that controls the movement of folate through various pathways in methionine synthesis. It allows for the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which donates an ethyl group to the metabolite homocysteine as it is being metabolized to methionine. The universal methyl donor S-adenosylmethionine is converted to S-adenosylhomocysteine when it donates a methyl group, and that compound can be hydrolyzed to homocysteine and adenosine [62, 63].

Hyperhomocysteinemia can be caused by dietary insufficiencies of folate, vitamin B12, or vitamin B6, as well as a mutation in the MTHFR gene [63]. Hyperhomocysteinemia leads to the elevated production of homocysteic acid, which excites neurons through agonism of NMDA receptors. These receptors have been shown to play a role in cortical spreading depression and aura, and researchers have shown that patients with migraine, with or without aura, have higher circulating levels of excitatory compounds such as glutamate, cysteic acid, homocysteic acid, and glycine [48, 61, 64]. This finding supports the notion that patients with migraine

have cortical hyperexcitability, and those with a mutation in the MTHFR gene, which can lead to hyperhomocysteinemia, may then have a higher likelihood of cortical hyperexcitability, thereby leading to potential migraine attacks. Studies have shown that patients with a mutation in the MTHFR gene, primarily the C677T polymorphism, may have an increased risk of migraine with aura [61, 63].

Patients with migraine or tension-type headache may have lower measured levels of vitamin B12 or hydroxycobalamin. Possible causes include chronic NSAID use in the setting of headaches, as well as other commonly comorbid gastrointestinal disorders, as these may impair vitamin B12 absorption or the production of intrinsic factor, which is necessary for B12 metabolism [61]. One study performed in Turkey evaluated the association between vitamin B12 deficiency and tension-type headache in 75 children under the age of 18. Sixty-two of the participants reported headaches less than 15 days a month, and 13 participants reported a headache frequency of greater than 15 days a month. This study found that patients with tension-type headache had significantly lower serum levels of B12 compared to controls, with the patients in the headache group having a mean serum level of 273.01 versus the control group level of 316.22 [65]. This study, however, did not look at whether B12 supplementation helped to alleviate headache severity or improve frequency.

A different study recently published in *Headache* in 2019 as a case-control evaluated serum vitamin B12 and methylmalonic acid levels (MMA) in patients with migraine. Researchers found that patients with migraine had significantly lower levels of B12 but higher levels of MMA compared to healthy controls [66]. Further analyses showed that those in the highest quartile of B12 levels were 80% less likely to have migraine, and those in the highest quartile of MMA levels had a five-times increased likelihood of having migraine [66]. However, there were no significant reported differences in the frequency, severity, or duration of migraine attacks in relation to the patients' measured serum B12 levels or MMA levels [66].

A 2015 study by Menon et al. evaluated dietary folate consumption in adult patients with migraine with aura. The study found that there was an inverse relationship between dietary folate intake and migraine frequency, but no significant relationship between the actual measured serum folate levels and the degree of migraine disability or severity [67]. These studies mentioned above have helped to foster research on whether supplementation of various vitamins involved in the metabolic pathways related to homocysteine and methylmalonic acid can affect migraine.

Two studies have been performed in patients with mutations in MTHFR who suffer from migraine with and without aura. The goal of these studies was to evaluate the role of folate and/or B12 supplementation in migraine prevention. Lea and colleagues conducted a 2009 randomized, double-blind placebo-controlled trial of patients with migraine with aura, some of whom had mutations in the MTHFR gene. Patients were given 6 months of a combination vitamin supplement comprised of folic acid 2 mg, vitamin B12 400 mcg, and vitamin B6 25 mg. In the treated patients, homocysteine levels were reduced by 39% compared to their baseline, and migraine disability reduced from 60% at baseline to 30% at the 6-month follow-up [63]. Participants in the treatment group also noted a decrease in

headache frequency and severity. Those with the MTHFR C allele genotype experienced a more significant response in these measures compared to the TT allele genotype. Thus, it was concluded that this subgroup of migraine with aura patients might benefit most from this type of vitamin supplementation [63].

The second randomized, double-blinded, placebo-controlled trial was conducted by Menon et al. in 2012, and included patients with migraine with aura who had MTHFR or MTRR genotypes (both are folate-related genes). Patients were given 6 months of a daily vitamin complex containing folic acid 2 mg, vitamin B6 25 mg, and vitamin B12 400 mcg. Those participants receiving the daily vitamin experienced a reduction in headache severity and migraine disability compared to placebo and had lower measures of serum homocysteine compared to placebo [68]. When looking at genotype, those who were C allele carriers of the MTHFR mutation had a higher reduction in homocysteine levels and a greater reduction in migraine severity and disability compared to the TT genotype [68]. These findings were similar to those reported in the study by Lea and colleagues in 2009. Additionally, the researchers found that those carrying the A allele of the MTRR A66G mutation had a higher reduction in homocysteine levels and a more substantial decrease in headache severity and disability. However, only the reduction in homocysteine level was statistically significant [68]. Secondary studies by the same research group did not find any reduction in homocysteine levels, migraine disability, or headache severity when 1 mg of folic acid was used in the vitamin supplement complex instead of 2 mg of folic acid [69].

A more recent study by Askari examined the utility of folic acid supplementation alone versus in combination with pyridoxine (vitamin B6) in the prevention of migraine attacks in patients with aura. This randomized, double-blind placebo-controlled trial included 95 adult participants with migraine with aura in Iran. Participants were randomized to receive either folic acid 5 mg daily plus pyridoxine 80 mg daily, folic acid 5 mg daily alone, or to placebo for 3 months. Results showed that those participants in the folic acid/pyridoxine group achieved a more significant reduction in headache attack frequency, duration, and severity compared to placebo and compared to the folic acid-only group. There was no significant difference in these measures when comparing the folic acid-only group to placebo [70]. The researchers concluded that the combination of folate and pyridoxine seemed to exert some benefit on migraine with aura attacks, but folate alone was not as successful at achieving this [70].

Vitamin B12 and folate supplementation generally does not cause any significant adverse events. In the Askari trial in 2016, two patients reported heartburn while taking the folate/pyridoxine combination [70]. The other aforementioned studies did not describe any adverse events in the groups receiving the vitamin. Though there are no formal recommendations or guidelines for usage, it seems that there is decent data to suggest that vitamin B12 and folate supplementation can be helpful for patients with headache who are deficient in those compounds. They can also be effective in reducing disability for patients with migraine with aura, especially those who possess the MTHFR gene mutation. Therefore, it is reasonable to consider folate and vitamin B12 supplementation for patients specifically with aura.

Pyridoxine (Vitamin B6)

Pyridoxine, or vitamin B6, plays a role in many metabolic reactions, but its role in migraine prevention is not entirely understood. Studies have alluded to pyridoxine playing a role in improving the "vascular events" that occur during a migraine, but this has not been elaborated on further [71].

A double-blind, RCT was conducted in Iran in 2015 to assess the utility of pyridoxine supplementation in the prevention of migraine. Patients with migraine with aura were either randomized to receive 80 mg of pyridoxine daily or placebo daily. The researchers found that those in the pyridoxine group experienced a decrease in headache severity (by two fewer points on a scale of one to ten) compared to placebo (who reported one fewer point in severity based on the same scale). The treatment group also experienced a reduction in the length of attacks, finding attack duration hours to be 8.3 less compared to 1.7 for those receiving placebo. However, participants receiving pyridoxine did not achieve a statistically significant reduction in the frequency of headache attacks when compared to placebo [71].

Researchers deemed pyridoxine to have a good tolerability profile at the doses studied. Only three patients in the study above experienced heartburn; otherwise no other side effects were reported. Pyridoxine is not routinely recommended for migraine prevention, but further studies may aim to elucidate its efficacy and safety profile further.

Omega-3 Fatty Acids

There has been some interest in investigating the role of omega-3 polyunsaturated fatty acids in the treatment and prevention of migraine. The mechanism by which omega-3 fatty acids may benefit migraine is likely an anti-inflammatory one. An increased intake of omega-3 fatty acids leads to a reduction of omega-6 fatty acids in inflammatory cells. It has been shown that lower levels of omega-6 fatty acids lead to a reduction in the production of arachidonic acid-derived prostaglandins that are pro-inflammatory and may be involved in migraine pathophysiology [72].

Two major published studies look to evaluate the utility of omega-3 fatty acids in migraine. The first is a meta-analysis of RCTs of omega-3 fatty acids. Five trials were included in the meta-analysis, with each investigating the efficacy of omega-3 fatty acid supplementation on the frequency and length of migraine attacks. Three of the included trials studied adults, one studied adolescents, and one evaluated the efficacy of omega-3 fatty acids in children. The meta-analysis found that omega-3 fatty acid supplementation did not affect the frequency or severity of migraine attacks in participants, but can reduce the duration of a migraine attack by about 3.44 fewer hours compared to placebo [72]. In general, the most common side effects of omega-3 fatty acids include nausea and eructation [72].

In a second study of patients with chronic migraine, 15 men and 16 women were randomized either to amitriptyline 10 mg with omega-3 (400 mg eicosapentaenoic acid and 350 mg of docosahexaenoic acid) versus amitriptyline 10 mg with placebo.

Researchers found that approximately 60% of patients in the omega-3 treated group had an 80% reduction in migraine days per month compared to approximately 30% of patients in the placebo group [73].

The AAN in 2012 ranked omega-3 fatty acids as level U, meaning there is insufficient evidence present to either support or refute its use in migraine (AAN Guidelines).

Ginkgolide B

Ginkgolide B is an herbal extract from Ginkgo biloba tree leaves. It is a potent antagonist of platelet activating factor (PAF), which is a pro-inflammatory factor that is released during inflammation and can lead to nociception by sensitizing trigeminovascular endings [74]. It is also reported to modulate glutamate transmission and scavenge free nitric oxide radicals. It is by these mechanisms that ginkgolide B is proposed to be useful in the prevention of migraine with and without aura.

A study by D'Andrea in 2009 evaluated the use of ginkgolide B with coenzyme q10 and vitamin B2 in patients with migraine with aura. Researchers found that patients taking the combination treatment prophylactically twice daily reported about two to two and a half fewer attacks over the four months (compared to four attacks at baseline). Patients also reported either resolution of aura or reduction in aura length while on the complex, and this was concluded to be from the ginkgolide B effects, as the coenzyme q10 and vitamin B2 components were in very low concentrations [74].

A second study by Esposito and colleagues found that children with migraine without aura taking a complex of ginkgolide B, coenzyme q10, riboflavin, and magnesium as a preventive agent reported five fewer days of headache per month during the study period [75]. This study was limited, however, given that the complex contained magnesium, riboflavin, and coenzyme q10, components that already have evidence for migraine prevention. Thus, it is unclear if the benefit was from these compounds or the ginkgolide B on its own.

The above studies did not comment on any specific adverse events, only mentioning that treatment was "well-tolerated." There have been no recent studies assessing the role of ginkgolide B in migraine prevention, and there are no current AAN guidelines for the use of ginkgolide B in headache treatment.

Ashwagandha

Ashwagandha, also known as Indian ginseng, is the root of *Withania somnifera*, which is an herb used traditionally in the Indian Ayurvedic system. It has been described to have neuroprotective, adaptogenic, and anti-inflammatory properties, amongst others. Studies in rats have shown that *Withania somnifera* root inhibits the development of morphine-induced hyperalgesia and prolongs the analgesia from

morphine, possibly mediated through binding to GABA and NMDA receptors, as it has a high affinity for these receptors [76]. This action on GABA and NMDA receptors may be a potential mechanism for how *Withania somnifera* exerts antinociceptive effects.

One study by Lopresti and colleagues found that patients taking daily ashwagandha extract reported lower anxiety and stress scores compared to placebo, suggesting ashwagandha may have anti-stress effects. The same study found that patients taking ashwagandha had reductions in morning cortisol levels and DHEA levels compared to the placebo groups. Researchers suggested that ashwagandha may exert its effects on the hypothalamic-pituitary-adrenal axis [77]. In this study, ashwagandha was well tolerated, and compliance was high. There were no reported differences between the treatment group and placebo group on laboratory measures of complete blood counts or lipid profile. There was no follow-up, so it is unclear if patients may experience a withdrawal syndrome after cessation of use [77].

An earlier study by Chandrasekhar and colleagues found similar results, with patients treated with ashwagandha achieving lower stress scores at all study points compared to placebo, with measured lower mean cortisol levels [78].

Though Ashwagandha may not directly improve headache, it may help to reduce stress, a common migraine trigger. This stress reduction may then indirectly lead to a reduced headache frequency. To date, there have been no studies examining the effects of *Withania somnifera* root on headaches in humans. Further research must be conducted before recommending this herb as a valid therapeutic option for migraine prevention.

Valerian Root

Valeriana officinalis is an herbaceous plant that has valerenic acids and flavonoids. Flavonoids inhibit cyclooxygenase enzyme, which may play a role in preventing the sensitization of pain receptors by inhibiting the synthesis of nitric oxide and prostaglandin E2 [79]. One study in female rats found that valerian root and turnip extract decreased acute pain sensation compared to controls, suggesting that the combination of both extracts may have anti-pain properties [79]. Though some data exists for valerian use for insomnia and anxiety in humans, there are no RCTs that assess its use for the treatment of headache.

Conclusions

Of the nutraceuticals mentioned, magnesium and riboflavin seem to have the most robust scientific evidence for use in migraine prevention. Some studies have suggested that melatonin, vitamin D, coenzyme q10, feverfew, and vitamin

E may be beneficial alternative therapies for migraine and other headache syndromes. Though Butterbur has good evidence for migraine prevention, further safety data is required. Boswellia, ashwagandha, and valerian root have minimal data in humans for headache prevention, but they may be good potential targets for future research. As patients often seek complementary and alternative therapies for their headache management, it is imperative to be aware of the many nutraceuticals that are available. Not all vitamins or herbal supplements are safe despite them being referred to as "natural" or "organic." Detailed, informed discussions with patients regarding efficacy and reported safety of these compounds are crucial to maintaining an evidence-based, well-informed, and prudent headache practice.

Summary of Nutraceuticals

Nutraceutical	Dosage	Side effects
Ashwagandha	Unknown	Drowsiness, may reduce anxiety and promote calmness, unknown long-term safety
Boswellia serrata	350 mg TID	Abdominal pain, diarrhea, indigestion, lightheadedness
Butterbur	50–75 mg BID	Potential liver toxicity, abdominal pain
Coenzyme Q10	100 mg daily, 100 mg TID	Anorexia, dyspepsia, nausea, diarrhea, rash
Essential oils	Topical application	Skin irritation, gynecomastia with repeated lavender use
Feverfew	50–300 mg BID	Mouth ulceration, dermatitis, GI symptoms, potential discontinuation syndrome, increased bleeding if on anticoagulation, stimulates uterine contractions
Ginkgolide B	60 mg daily	Unknown, possible GI upset and dizziness
Magnesium	400–600 mg daily	Soft stools, flushing, GI discomfort
Melatonin	3 mg–20 mg nightly	Drowsiness
Omega-3 fatty acids	400 mg EPA + 350 mg DHA daily	Nausea, eructation
Riboflavin	200 mg BID/400 mg daily	Fluorescent urine
Valerian root	Unknown	Drowsiness
Vitamin B6	80 mg daily	Heartburn
Vitamin B12/ folate	400μg daily/2 mg daily	Nervousness, itching, swelling; abdominal cramping, diarrhea, rash, irritability, nausea
Vitamin E	400 IU daily	High levels may increase bleeding risk
Vitamin D	1,000 IU daily, or 50,000 IU weekly	Hypercalcemia – GI upset, weakness, polyuria, confusion
5-HTP	300 mg daily	Epigastric pain, urticaria, allergy, diarrhea, weight gain

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Chapter 10
Neuromodulation

Huma U. Sheikh

Introduction

Neuromodulation or neurostimulation fills an important unmet need for abortive and preventive therapy in migraine as well as other primary headache disorders. It can be a good option when patients have inadequate relief with or contraindications to pharmaceuticals. Neuromodulation can be used either as a primary mode of treatment or as an adjunct therapy [1]. It can serve as an abortive or as a preventative strategy. The most common acute medications used are triptans or nonsteroidal anti-inflammatory drugs (NSAIDs). However, there is a high discontinuation rate with triptans and NSAIDs, usually due to a lack of efficacy or adverse effects [2].

There is evidence that neuromodulation can be helpful in several types of primary headache disorders, including migraine and cluster headaches. The basic concept behind neuromodulation is to manipulate peripheral or central pain pathways with either magnetic or electrical impulses [3].

Neuromodulation comes in a variety of forms, including invasive, minimally invasive, or noninvasive devices. Neuromodulation was first introduced with deep brain stimulation of the hypothalamus [4]. Over time, other neuromodulation techniques have been developed that are now minimally or noninvasive options. While patients can use some neuromodulators at home without any prior medical interventions, others require surgical implantation. Neuromodulation as a treatment modality is safe and well-tolerated, although each form carries its specific risks and potential adverse effects [1]. A summary of neuromodulation techniques can be found in Table 10.1.

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Table 10.1 Summary of neuromodulation techniques

Neuromodulation type	Headache type	Study design	Sample size	Efficacy	Side effects
Deep brain stimulation	Cluster	Randomized prospective crossover double-blind	11	In the 1-year open-label phase, about 50% of patients responded, 50% decrease in the frequency of attacks	Electrode displacement, infection, one death by ICH
Occipital nerve stimulation	Cluster	Pooled analysis of nine studies	91	Average of 67% reduction in headache frequency	
	Chronic migraine	Randomized sham-controlled	61	50% monthly reduction in headache days or >3 point reduction in pain	
Sphenopalatine ganglion stimulation	Cluster	Multicenter randomized sham-controlled	28	Pain relief at 15 minutes 67% of the time	Lead revisions, sensory disturbances
	Cluster	Randomized, sham-controlled parallel-group, double-blind	93	63% had pain relief in 15 minutes	Infection
sTMS	Migraine abortive	Multicenter randomized double-blind sham-controlled	82	Higher pain-free at 2 hours, sustained results at 24 and 48 hours	
	Migraine prevention	Open-label observational	132	Reduction of 2.75 headaches	Lightheadedness, tinnitus, tingling
tSNS	Migraine prevention	Multicenter, randomized, sham-controlled, double-blind	67	Mean number of migraine days was reduced by almost 7 days	
	Migraine abortive	Randomized, sham-controlled, double-blind	106	Pain intensity at 1 hour was reduced	Paresthesias, nausea

(continued)

Table 10.1 (continued)

Neuromodulation type	Headache type	Study design	Sample size	Efficacy	Side effects
VNS	Chronic migraine prevention	Prospective, multicenter, double-blind sham-controlled	59	Decrease in mean headache days but not statistically significant	URI, GI
	Episodic migraine prevention	Multicenter double-blind, randomized sham-controlled	322	Not statistically significant	
	Migraine abortive	Prospective, double-blind sham-controlled	248	Pain improvement and pain freedom at 30 and 60 minutes did not meet pain freedom at 120 minutes	
	Cluster abortive	Sham-controlled double-blinded, randomized	242	Did not meet reduction in pain at 15–60 minutes	
	Cluster prevention	Open-label randomized	97	Reduction in number of attacks	
REN	Migraine abortive	Randomized, double-blind, sham-controlled, multicenter study	100	Significant benefit for pain relief at 2 hours	Numbness, warmth at site of stimulation

Invasive Treatments

Examples of invasive neuromodulation techniques include deep brain stimulation and occipital nerve stimulation. These techniques are discussed in further detail above.

Deep Brain Stimulation

Deep brain stimulation (DBS) has been used mainly for cluster headaches. Studies have shown that the posterior hypothalamus plays a role in cluster headaches [5], later further organized specifically to the ventral tegmental area [6]. DBS is usually reserved for patients who do not respond to conservative therapy, given its invasive nature [7]. The theory of DBS is based on the fact that electrode stimulation reduces hypothalamic activation during cluster attacks.

For DBS, a typical neurostimulator consists of a battery pack, extension wire, and an electrode. The battery is implanted under the skin near the collarbone. The wire extends under the neck and shoulder, with the tip positioned toward the hypothalamus. A titanium electrode is inserted into the ventral tegmental area ipsilateral to the site of the pain [8]. The stimulator can be turned on and off as needed.

A randomized prospective crossover, double-blind with sham study in 11 patients was conducted in 2018 [9]. Patients had posterior hypothalamic stimulation with a frequency of 185 Hz and a pulse duration of 60 ms. There was no initial difference between active and sham; however, in the 1-year open-label phase, a little over half of the patients did respond to the chronic stimulation with a 50% decrease in the frequency of attacks. There were also no differences in adverse events [9].

There are more open-label studies, now with a combined total of about 60 patients. Overall, there is about a 66% response rate in the treatment of chronic cluster headaches [10]. Most of the data shows that the effect is present when there is long-term hypothalamic stimulation for the prevention of attacks. There is no evidence that DBS helps acutely [3].

There are some distinct disadvantages to DBS, given that it is an invasive procedure with hardware implanted in the brain. Some of the possible adverse events include electrode displacement, infection, pain along the lead, and complications during the implantation of the device [11]. There have been reports of hunger and libido changes as well as a case of death by intracerebral hemorrhage [12]. Given its invasive nature, DBS is usually considered in the most refractory of cases, including those with daily cluster attacks who have failed less invasive treatments, including medications [11]. DBS is currently not used for migraine or other primary headache disorders.

Occipital Nerve Stimulation

Occipital nerve stimulation (ONS) is another form of neuromodulation, which requires surgical intervention. The target for ONS is the peripheral occipital nerve, which is believed to have sensory afferents that converge on the second-order nociceptors in the trigeminocervical complex [3]. Stimulation of the occipital region modulates pain in the trigeminal distribution by inhibiting nociceptive activity in the small c-fiber and A-delta fibers [11]. There is also thought to be a central mechanism where ONS affects the areas in the pain processing centers of the brain [13]. ONS has been studied in migraine, cluster, hemicrania continua, and short-lasting unilateral neuralgiform headache attacks [10]. Like deep brain stimulation, ONS is reserved for the most refractory of cases given that it is an invasive procedure and needs to be done by experienced surgical teams.

The occipital nerve stimulator has electrodes that are placed subcutaneously above the greater occipital nerve. They are wired to a battery pack with adjustable stimulation parameters [3]. Most of the time, the electrodes are placed bilaterally. Studies have shown that, with unilateral leads, the side of the pain can shift contralaterally [3]. It is programmed to be on continuously and not adjusted during attacks

while achieving a comfortable level of paresthesia in the distribution of the greater occipital nerve. Results are typically seen after about 3 months [3].

Chronic Migraine

There have been three randomized sham-controlled trials looking at occipital nerve stimulation for the treatment of chronic migraine. The Occipital Nerve Stimulation for the Treatment of Chronic Migraine Study examined 61 patients comparing adjustable and preset stimulation, along with medical management [14]. There was a positive response in the adjustable groups with a 50% monthly reduction in headache days or a >3 point reduction in pain scores [14]. Two other randomized trials did not have significant outcomes [15, 16]. However, a pooled analysis of the three trials did show a mean reduction of 2.59 migraine days per month after 3 months compared with sham controls [17].

Occipital Neuralgia

Given that the stimulator is placed near the occipital nerve, it is used for the medical condition occipital neuralgia (ON). ON often accompanies migraine but can also be a phenomenon that presents on its own. One case series of 13 patients with intractable occipital neuralgia had stimulation at the occipital nerve trunk at the level of C1. Patients were followed for 2 years, and about two-thirds had responses at greater than >75% pain relief [18].

Cluster Headache

There are no randomized trials in cluster headache; however, a prospective, randomized control trial is currently in progress in Europe [19]. One review paper did a pooled analysis of nine published studies for the use of ONS in cluster headache. These included a total of 91 patients and found that there was an average of 67% reduction in headache frequency [10]. There is an open-label study that included 35 chronic drug-resistant cluster headache patients. They were followed for 6 years, and about two-thirds had a greater than 50% reduction in headache numbers per day [20]. Another study with 51 chronic cluster headache patients had ONS implanted, and they were followed over 3 years. At the end of follow-up, the overall response rate was about half for at least a 50% improvement in attack frequency [21].

Other Primary Headache Disorders

The study mentioned above also included other headache types. In addition to the 51 chronic cluster patients, this open-label prospective study of 100 patients also included those with chronic migraine, short-lasting unilateral neuralgiform

headache, and hemicrania continua. It showed that those with pain in the occipital region, as well as pre-existing anxiety or depression, were the most likely to respond to ONS [21].

Although ONS is relatively safe, it is still an invasive procedure and usually implanted by a neurosurgeon. There are risks, including the potential for lead migration, infection, paresthesias, or battery depletion [3].

Minimally Invasive Treatments

Sphenopalatine Ganglion Stimulation (SPGS)

In this procedure, the target of neuromodulation is the parasympathetic sphenopalatine ganglion (SPG). It is an extracranial parasympathetic ganglion in the pterygopalatine fossa, which can be accessed relatively easily through a minimally invasive approach [22]. It is thought that the SPG is involved in the modulation of sensory processing in the trigeminal nucleus caudalis and stimulation interrupts the postganglionic parasympathetic signals of pain [22].

The SPG stimulator is placed through the mouth into the posterior maxillary mucosa, usually ipsilateral to the side of pain. It is positioned as proximal to the SPG as possible and used in many headache types [3]. SPGS has been studied in a few primary headache disorders, including cluster and migraine.

A multicenter, randomized, sham-controlled clinical trial evaluated 28 patients with chronic cluster who used the stimulation at the time of moderate to severe pain. It showed that SPG stimulation had pain relief at 15 minutes 67.1% of the time versus 7.4% in the sham, which was significant. It also showed that there might be a preventive effect from the SPG stimulation. The main adverse effects were the need for lead revisions and sensory disturbances, as well as facial pain, swelling, hematoma, and infection [23]. Other reported side effects are temporary numbness in the maxillary nerve region and persistent mild sensory changes and pain in the area of the SPG implant [7, 23].

A large recent randomized, sham-controlled, parallel-group, double-blind study was published in December 2019 with a total of 93 patients in 21 headache centers in the United States. It showed that about 63% of patients had pain relief at 15 minutes compared to 39% in the control group, which was significant. There was one serious adverse event, which was an infection [24]. A paper by Tepper and Caparso in 2017 reviewed a randomized controlled trial, open-label trial extension, and registry of patients and found that the success rates show two-thirds being responders [25].

Given that it is also invasive, an expert consensus in 2014 for the use of SPG in chronic cluster recommended its use in medically refractory cases. It should be implanted in a specialty center. The leads are implanted, and then an external device is placed over the cheek during attacks or, in some cases, as a preventive at regular intervals [3].

Noninvasive Treatments

Transcranial Magnetic Stimulation (TMS)

TMS is a noninvasive method to deliver neuromodulation. Currently, there are two types of TMS that are in use: repetitive and single-pulse [26]. TMS delivers electric currents to the layers of the scalp, skull, meninges, and cerebrospinal fluid and into the superficial layers of the cortex [27]. It is believed that it is then able to modulate the electrical environment of the neurons. Single-pulse TMS (sTMS) is thought to inhibit cortical spreading depression and help in acute attacks. Some studies have also shown that sTMS can inhibit the activity of the nociceptive thalamic trigeminovascular neurons, thought to be involved in the development of central sensitization [28]. Repetitive TMS is believed to alter the cortical hyperexcitability depending on the frequency, location, and strength of the stimulation and may help with prevention [11].

The best evidence for sTMS came from a multicenter, randomized, double-blind, sham-controlled trial. It involved a portable, handheld device that patients used to evaluate the acute treatment of migraine with aura. There were 82 patients in each arm; all of them had migraine with aura. The sTMS group showed a statistically significant proportion of subjects that were pain-free at 2 hours, which was the primary outcome measure, compared to the placebo. The sTMS device also showed sustained results at 24 and 48 hours, better than sham control. There were no serious adverse events. This trial led to the approval of sTMS by the Food and Drug Administration (FDA) for the acute treatment of migraine with aura [29].

After it was available in the market, post-marketing revealed that the device was not only helpful in acute migraine but also beneficial as a preventive treatment, in both episodic and chronic migraine, as well as in patients with migraine without aura [30]. This finding was based on a multicenter, prospective single-arm open-label study examining sTMS as a preventive treatment. Patients were surveyed over 3 months, with a total of 190 patients. Sixty-two percent reported pain relief with the device, either alleviating or reducing migraine pain, along with improvements of associated features, like nausea and photophobia. There was a reduction in the total average number of headaches in both the episodic and chronic migraine categories [30].

Another open-label observational study looking at sTMS for the prevention of migraine was done with 132 patients. They used the sTMS device, four pulses twice daily as prevention and an additional three pulses, up to three times a week as needed as an abortive. It showed a reduction of 2.75 fewer headache days in the sTMS group, which was statistically significant. Forty-six percent achieved a 50% responder rate and used close to 3 fewer days of acute medications. The most common side effects were lightheadedness, tinnitus, and tingling [31].

sTMS was first approved for the acute treatment of migraine in 2014 and then for preventive treatment in 2017. In early 2019, sTMS was FDA approved for abortive and preventive therapy of migraine in patients over 12 years of age [32].

Transcranial magnetic stimulation has been used in other conditions for many years and therefore has a significant track record of safety. sTMS is well tolerated in migraine and has no severe side effects, although it is contraindicated in patients with epilepsy [33]. There are some reports of breakthrough seizures in TMS. There is also

a risk of lead migration or current induction in subjects who have metal in their body, including those with pacemakers, defibrillators, or other implanted stimulators [34]. It is ideal in patients who have contraindications to acute oral agents, including patients with cerebrovascular or cardiovascular disease. It is also an attractive option during pregnancy and preconception, although there are no specific studies in this population. In the post-marketing study of sTMS, three pregnant women used the device and had no labor or delivery complications and delivered healthy children [30].

Using the sTMS mini is as easy as 1, 2, 3

Step 1: Power

Pree the center button to turn on the sTMS mini.

When the green racetrack is fully illuminated, you're ready to treat.

Step 2: Position

Hold the sTMS mini so it cradles the back of your skull.

Step 3: Pulse

Press one or both of the treatment buttons to deliver a safe therapeutic pulse.

Repeat steps as prescribed.

From the eNeura website – http://www.eneura.com/getting-started-with-the-stms-mini/

Transcutaneous Supraorbital Neurostimulation (tSNS)

Transcutaneous supraorbital neurostimulation (tSNS) is a neuromodulation device that targets the supraorbital nerve (SON) and likely the supratrochlear nerve (STN), which are branches of the frontal nerve [11]. With this device, the adhesive electrodes are placed on the forehead, where the SON and STN provide sensation. The device sends electrical impulses to these peripheral nerves, and it is thought to help in migraine by inhibition of nociception in the pain-transmitting fibers that, in turn, modulate activity in the trigeminal ganglion. It also likely has an effect on central neuromodulation and antinociceptive activity in the anterior cingulate cortex [11, 35].

There was a multicenter, randomized, sham-controlled, double-blind trial of tSNS as migraine prevention. Participants were instructed to treat daily for 20 minutes a day. There were a total of 67 patients, and the mean number of migraine days was significantly reduced in the treatment arm, about 6.94 days less compared to sham, which was 4.88 days. The treatment group was also more likely to have at least a 50% reduction in migraine days per month vs. sham. The study did not, however, meet the primary endpoint. There were no reported adverse effects in either group [36].

There was an open-label trial, including 19 patients with chronic migraine who completed the study over 4 months. Eight patients achieved both primary endpoints, which were 50% reduction in monthly migraine days and a 50% reduction in monthly acute medication use. Three patients dropped out due to adverse effects [37].

The study that looked at tSNS for acute treatment was published in 2019. It was a single randomized, sham-controlled, double-blind study, called the ACME trial [38]. There were a total of 106 patients who treated an attack for 1 hour. The primary outcome was the mean change in pain intensity at 1 hour using the 1–10 visual analog scale. The primary outcome was met, and the device was well tolerated without serious adverse effects. Some of the minor side effects were paresthesias and nausea. tSNS is approved for the acute and preventive treatment of migraine. The current device is rechargeable and applied to the forehead [3].

Vagal Nerve Stimulator (VNS)

Vagal nerve stimulation is a noninvasive treatment modality using a handheld device that sends a mild electrical current to the vagus nerve. The vagus nerve is a motor and sensory nerve and has some projections to the area of pain regulation [3]. Stimulation of the vagus nerve has been used previously to treat other disorders, including epilepsy and depression. It was noticed that comorbid headache also was improved in these patients, and therefore it was later studied in primary headache disorders [3, 39]. VNS is thought to work by an inhibitory effect on structures involved in central sensitization and possibly in the release of glutamate in the

trigeminal nerve as well as reduction of cortical spreading depression [7]. The handheld device sends electrical stimulation to the cervical or auricular branch of the vagal nerve while positioned over the neck.

Migraine

The primary evidence for its efficacy in migraine was the EVENT study, which was a prospective, multicenter, and double-blind sham-controlled study with chronic migraine patients using the noninvasive vagal nerve stimulation (nVNS) for prevention. Subjects were given two 2-minute stimulation, three times a day for 2 months [40]. There were a total of 59 patients in the treatment and control group. There was a reduction in mean headache days, confirmed on the open-label extension of the same study, but the study was not statistically powered. The main adverse effects were upper respiratory tract infections and gastrointestinal symptoms [40].

There was one positive trial for acute treatment using the vagal nerve stimulator, the PRESTO trial, that was prospective, double-blind, and sham-controlled using the nVNS for the acute treatment of episodic migraine attacks. There were a total of 248 subjects who were advised to use the device within 20 minutes of migraine onset, with the option to repeat in 15 minutes. While it did not meet its primary endpoint of pain freedom at 120 minutes, there was pain improvement, and it was statistically significant for pain freedom at 30 and 60 minutes of use, but not for 120 minutes [41].

The PREMIUM trial was published in October 2019, which was a multicenter, double-blind, randomized sham-controlled trial for the preventive treatment of episodic migraine. There were a total of 322 subjects in the intention-to-treat group, but the primary outcome of a reduction in migraine days per month was not statistically significant. It is possible that the sham also provided vagus nerve stimulation, although post hoc analysis did show a significant effect in the treatment group [42].

Cluster Headache

There is also evidence that nVNS is beneficial in cluster headache. There was an initial open-label pilot study, including 11 patients with chronic cluster and 8 patients with episodic cluster headaches. Subjects used the device for acute attacks, and 47% of the attacks ended within 11 minutes [43]. Another open-label, randomized control trial of 97 patients added on nVNS as a preventive to their usual therapy. There was a reduction in the number of attacks compared to sham with no serious adverse effects [44].

There were a pair of sham-controlled, double-blinded, randomized control trials for the abortive use of nVNS in cluster headaches. These were the ACT1 and ACT2 trials. Subjects used the nVNS for 2 minutes for an attack, up to three times. The primary endpoint was mild or no pain at 15–60 minutes after treatment, which did

not meet statistical significance. There was significance in the episodic group when subjects were stratified to either episodic or chronic cluster [45, 46].

Other Primary Headaches

There are also studies using nVNS for indomethacin-responsive headaches. Fifteen subjects used the device, nine with hemicrania continua and six with paroxysmal hemicranias, either as primary or adjunct therapy. In those with hemicrania continua, 78% of hemicranias showed reduced severity of continuous pain. In paroxysmal hemicranias, about 67% of patients showed some improvement. There was some degree of benefit in everyone [47].

The FDA has approved nVNS for both migraine and cluster headache. It is FDA approved for both the acute treatment of episodic cluster attacks and as an adjunct therapy for cluster prevention. It is currently FDA approved only for abortive treatment in migraine in adults.

Like some of the other noninvasive neuromodulation devices, nVNS is considered safe and well-tolerated. There are some reports of a stiff neck, shoulder pain, facial drooping, and frequent urination. There are also some reports of associated neck twitching or redness at the site of stimulation. There are no cardiovascular-related adverse events noted. It is, however, contraindicated in patients with implantable medical devices, like pacemakers and defibrillators, as well as in those with carotid atherosclerosis or significant hypertension, hypotension, bradycardia, or tachycardia [3, 11].

Remote Electrical Neuromodulation (REN)

One of the newest treatments that have come out in the neuromodulation field is remote electrical neuromodulation (REN). This is a novel neuromodulation technique that has been approved by the FDA and is available for use in the population.

In this treatment, the peripheral nerves in the upper arm are stimulated, which is thought to work through a concept known as conditioned pain modulation (CPM). The device was built from a known natural mechanism for analgesia, in which stimulation in one area of the body inhibits pain in a remote body region [48]. This, in turn, activates descending inhibition pathways. These begin in the periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) and work by releasing the neurotransmitters, serotonin, and noradrenaline [48].

The most recent randomized, double-blind, sham-controlled, multicenter study was published in 2019 to evaluate the efficacy and safety of REN in the acute treatment of migraine [49]. The study was conducted at 12 sites, 7 in the United States and 5 in Israel, from December 2017 to October 2018. Patients with episodic migraine (<12 headache days per month) were included, with several exclusion criteria including pregnancy, nursing, and those who had received onabotulinumtoxinA in the prior month or nerve blocks in the preceding 2 weeks [49].

The device used was the Nerivio Migra® Theranica Bio-Electronics Ltd., Israel, REN device. It is a wearable battery-operated unit that is controlled by a smartphone application. It is placed on the lateral upper arm at the bellies of the lateral deltoid triceps, meant to stimulate only the nerves in the skin. Patients were asked to treat their migraine attacks for 4–6 weeks by using the device for 45 minutes, beginning within an hour of onset of their migraine.

The primary endpoint was pain relief at 2 hours post-treatment, with a few other secondary endpoints as well. There were a total of 100 patients in each group, REN and sham control. The REN was found to have a significant benefit for the primary endpoint as well as a couple of the other secondary endpoints [49].

REN is a new method of using neuromodulation in comparison to the other neuromodulation devices available. The other devices stimulate the head or neck, which triggers a local response. TMS inhibits cortical spreading depression, while vagal stimulation activates the autonomic-somatic inhibitory interaction. REN uses the CPM theory to inhibit pain [50]. The main adverse effects include warmth at the site of stimulation and numbness in the arm/hand [49].

Upcoming Techniques

Auricular noninvasive vagal nerve stimulation (auricular t-VNS) uses an ear electrode to stimulate the vagal nerve. There is one prospective, double-blind parallel-group trial on adult subjects with chronic migraine, which did show a more significant decrease in headache days in the treatment group. However, there were no changes in secondary endpoints [51]. It is not currently available.

Transcranial direct current stimulation (tDCS) is a device that uses a portable, handheld device to help with pain relief. In a trial of 30 patients who received 10 procedures during a month of stimulation over the dominant hemisphere, there was no change in mean monthly days of headache [52].

Transcutaneous occipital nerve stimulation (tONS) uses a concept similar to tSNS for migraine prevention. It was tested against topiramate with a similar decrease in headache duration. It was well tolerated, but more studies are needed [53].

Caloric vestibular stimulation (CVS) is another neuromodulation technique that was studied in a parallel-arm placebo-controlled trial for the prevention of episodic migraine, using CVS twice a day for 3 months. There was a significant decrease in the primary endpoint of fewer days of migraine [54].

Conclusion

For most devices, FDA clearance is based on safety and not necessarily proven efficacy, which sometimes allows for devices to be approved even without large randomized control trials. Despite that, many of these minimally or noninvasive

neuromodulation techniques allow for treatment alternatives for those who have contraindications or previous failures to other abortive and preventive options.

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Chapter 11
Interventional Treatment of Head and Neck Pain

Amir Abdel-Kader and Yury Khelemsky

Introduction

This chapter reviews the anatomy, procedural considerations, and evidence base for procedures commonly employed to treat head and neck pain.

Trigeminal Nerve and Trigeminal Ganglion

Trigeminal Nerve and Trigeminal Ganglion Anatomy

The trigeminal nerve, the largest and arguably most complex of the cranial nerves, provides sensation to the face and head and is responsible for the motor function of the muscles of mastication. The sensory portions of its three major branches (e.g., ophthalmic nerve/V1, maxillary nerve/V2, and mandibular nerve/V3) arise from the trigeminal (e.g., Gasserian or semilunar) ganglion, located in Meckel's cave. From the ganglion, fibers continue centrally to the pons to reach the trigeminal nucleus caudalis (TNC), which extends caudally to connect with C1, C2, and C3 segments of the spinal cord. The TNC also sends nerve fibers to the thalamus, hypothalamus, and autonomic nucleus in the pons. *This pathway, known as the trigeminocervical complex (TCC), has been extensively studied in animal models* [1–3] *and is a basis for migraine-associated pain in the neck and back of the head* [4].

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Peripherally, the major branches of the trigeminal nerve further divide into numerous smaller branches, of which the relevant ones to this chapter include supraorbital nerve (SON), supratrochlear nerve (STN), infraorbital nerve (ION), zygomaticotemporal nerve (ZTN), auriculotemporal nerve (ATN), inferior alveolar nerve (IAN), and mental nerve.

Trigeminal Ganglion Block Technique

A traditional trigeminal ganglion nerve block is performed with the patient in a supine position under fluoroscopic guidance with a 22- to 25-gauge needle. First, an anterior-posterior image with a steep cephalad tilt is taken for a submental view and visualization of the foramen ovale. The needle, while aligned directly inferior to the pupil on the ipsilateral side of pain, is then inserted either intraorally or percutaneously 2 to 3 cm lateral to the corner of the mouth. The needle is directed toward the base of the skull and posteriorly around 6 to 8 cm until it enters the foramen ovale. A lateral image is then taken to confirm the location and contrast is injected. Aspiration of CSF has been historically considered a positive sign of entry into Meckel's cave. Injection of local anesthetic would then proceed. However, some proceduralists may choose not to proceed with an injection if a dural puncture inferior to the temporal lobe is suspected [5]. Complications of this procedure include ophthalmic nerve block, mandibular nerve block, cerebrospinal fluid leak, paresthesias, nerve injury, or damage to the temporal lobe or brainstem.

Due to the difficulty in placement and risk of complications, the use of the lateral coronoid approach (Fig. 11.1) to this block has largely replaced the traditional approach. With this approach, the mandibular and maxillary nerves can also be selectively blocked. This approach is performed in a similar manner to the traditional one, with the patient in a supine position and under fluoroscopic guidance. The coronoid process of the mandible is the main anatomic landmark. After palpation and fluoroscopic identification of this structure, the needle is inserted cephalad with a superior-anterior tilt in a lateral to medial direction toward the lateral pterygoid plate. After contact is made with the lateral pterygoid plate with the advancement made under fluoroscopic guidance, the needle is withdrawn slightly (2 mm), and contrast is injected to confirm the location. An injectate of 5 to 10 mL of a local anesthetic/steroid mixture will block the maxillary and mandibular nerves for maxillary and mandibular neuralgias. To specifically target the trigeminal ganglion, additional steps must be taken. After contact is made with the lateral pterygoid plate, the needle is directed in a postero-inferior direction to slide under the lateral pterygoid plate and is advanced approximately 1 cm [6]. The location is confirmed with contrast at this point, and the injectate is then placed. Complications of this technique include hematoma, nerve injury, and nerve compression. The ophthalmic nerve root is avoided with this approach, so there is no risk of visual complications.

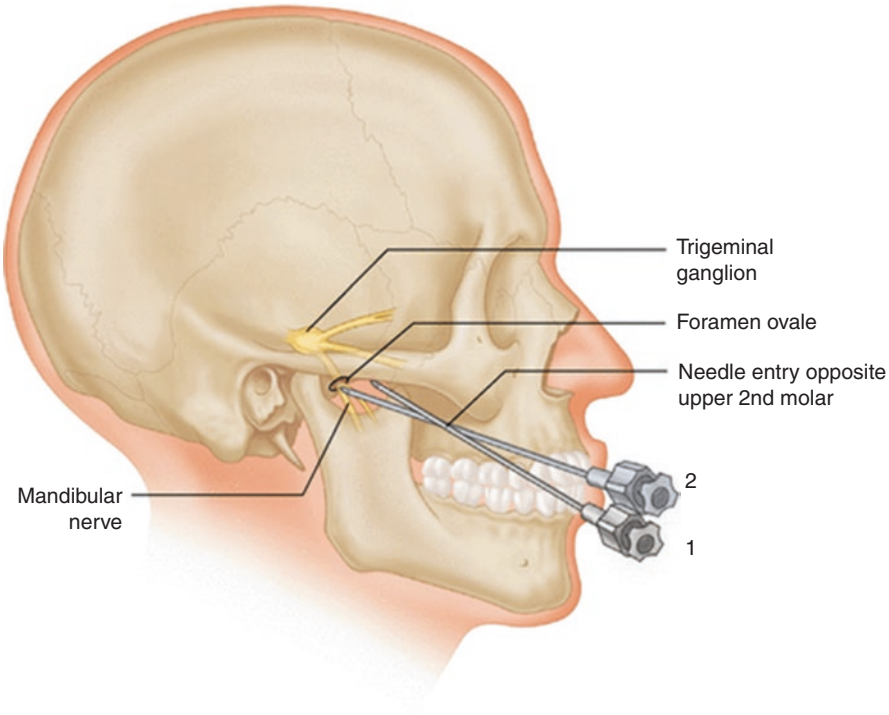

Fig. 11.1 Lateral coronoid approach for trigeminal nerve block

Trigeminal Ganglion Treatment Evidence

Trigeminal neuralgia, or *tic douloureux*, is characterized by brief, but sudden episodes of intense facial pain in the distribution of the trigeminal nerve branches thought to be caused by external compression of the ganglion. Medical therapy, often with carbamazepine, is considered first-line treatment for trigeminal neuralgia, while neurolysis, ablation, and surgical techniques are reserved for refractory cases.

Although no large randomized control trial has been conducted comparing the various neurolytic treatments, radiofrequency ablation, with either the traditional or pulsed variety, is an effective method of treatment for trigeminal neuralgia with traditional radiofrequency reported as superior to pulsed radiofrequency for analgesia and decreased pain recurrence [7]. Other techniques, including balloon compression and glycerol gangliolysis, have also been shown to provide excellent relief [8]. High-voltage pulsed radiofrequency has been shown to be more effective than standard-voltage pulsed radiofrequency at 1-year post-procedure, with effective rates of success of 69% in the high-voltage group compared to 19% in the

standard-voltage group [9]. The combination of conventional and pulsed radiofrequency treatment also demonstrated success in patients afflicted with refractory trigeminal neuralgia, as demonstrated in a retrospective study [10].

Supraorbital Nerve (SON) and Supratrochlear Nerve (STN) Anatomy

The frontal nerve, the largest branch of the ophthalmic nerve and often considered the continuation of it, enters the orbit through the superior orbital fissure and divides into two branches, the supraorbital nerve (SON) and the supratrochlear nerve (STN). The SON exits the orbit through the supraorbital foramen and provides sensation to the forehead, scalp, upper eyelid, and frontal sinus. The STN exits more medially through the supraorbital notch and provides sensation to the bridge of the nose, medial portion of the upper eyelid, and the medial portion of the forehead.

SON and STN Block Techniques

The SON block is done with the patient in a supine or sitting position with a 25- to 30-gauge 0.75- to 1.5-inch needle. The supraorbital notch is first palpated in the mid-pupillary line (Fig. 11.2). The needle is inserted either perpendicularly to the skin or in a medial or lateral approach with the area immediately superior to the supraorbital notch as the target. Care must be taken not to insert the needle into the supraorbital foramen to prevent paresthesia or hematoma. The frontal bone should be contacted with the needle. After negative aspiration, the injectate is placed, and external manual pressure is held at the inferior border of the frontal bone to prevent local anesthetic from tracking down into the eyelid or orbit [11]. Complications include orbital trauma or deformity, periorbital hematoma or infection, and weakness of extraocular muscles.

The STN block is also performed with the patient in a supine position with a 25- to 30-gauge 0.75- to 1.5-inch needle. The supraorbital ridge at the medial aspect of the corrugator muscle is palpated, and the needle is inserted perpendicularly into the skin in the muscle. The frontal bone should be contacted with the needle. After negative aspiration, the injectate is placed, and external manual pressure is held at the inferior border of the frontal bone to prevent local anesthetic from tracking down into the eyelid or orbit. An alternative approach to this technique is to perform a field block along the frontal bone above the level of the orbit and medial to the supraorbital foramen [12]. Complications are similar to that of the SON block mentioned above.

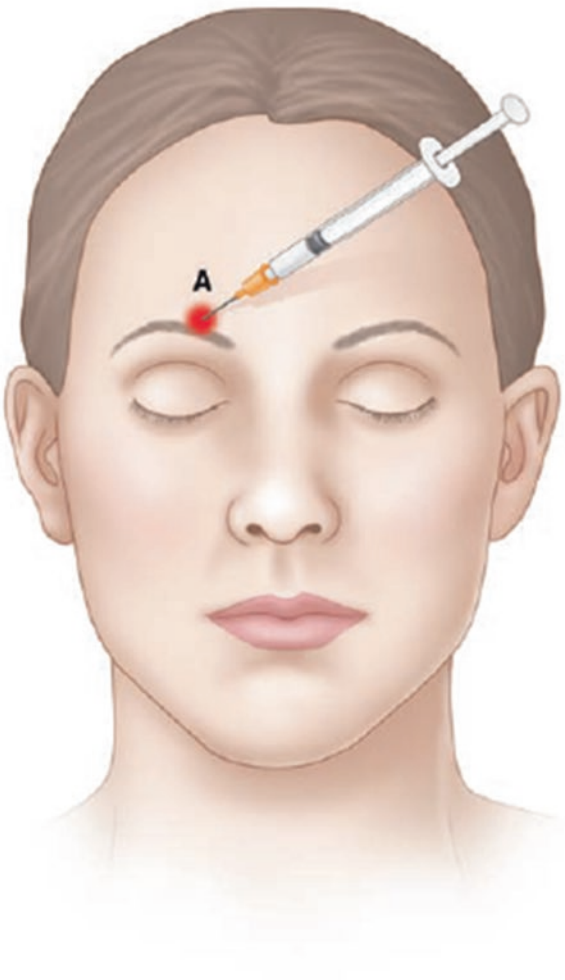

Fig. 11.2 Supraorbital nerve block

SON and STN Treatment Evidence

Entrapment of the SON as it exits the foramen, usually caused by direct trauma and swelling, can lead to unilateral headaches associated with throbbing, photophobia, and auras, sharing symptoms of migraine or hemicrania continua (HC). *Furthermore, this nerve, as all branches of the trigeminal system, can be sensitized by continued nociception produced by primary headache disorders and, after being sensitized, can independently contribute to the headache pain, as well as potentially act as a*

trigger for the propagation of the primary headache. Non-medical treatment of supraorbital neuralgia includes nerve injections, neuromodulation, and ablative techniques.

Successful treatment of patients with hemicrania continua (HC) using injections of both the SON and GON has been shown, with tenderness to palpation at the nerve sites as the inclusion criteria for the report [13]. Consequently, nerve blockade can be offered to patients with intolerance to indomethacin, with evidence of successful partial treatment of HC having been demonstrated [14]. In patients with supraorbital neuralgia, this blockade often shows complete resolution of symptoms [14]; hence, there is utility in using this technique for diagnostic measures when HC and/or supraorbital neuralgia are suspected.

Neuromodulation with SON and TON stimulation is an effective treatment for various types of headaches, with the technique gaining popularity in recent years. SON neuromodulation was described in 2007 when a patient with chronic cluster headache was successfully treated with a percutaneous electrode providing stimulation at his site of pain [15]. Patients with trigeminal autonomic cephalalgia (TAC) have also been successfully treated with implantations of a neuromodulation system of the SON and TON. It is important to note that SON blocks do not always accurately predict the response to neuromodulation [16]. Therefore, a trial of neuromodulation may still be considered after an unsuccessful nerve block.

Chronic frontal and temporal neuritis [17], chronic migraine [18], craniofacial pain [16], and chronic cluster headache [15, 19] have also been reported to be successfully treated with either SON neuromodulation or a combination of SON and GON neuromodulation.

Irritation and/or entrapment of the STN, sometimes due to compression by poor-fitting eyeglasses, often presents as midline forehead pain. Other causes for supratrochlear neuralgia include cranial trauma, surgery, or varicella infection [20]. While uncommon, isolated supratrochlear neuralgia can be clinically diagnosed and differentiated from other conditions by the presence of local tenderness upon palpation at the site of nerve emergence (medial one-third portion of the upper orbital rim) [20]. Successful long-term treatment of patients with supratrochlear neuralgia has been achieved with single or multiple STN blocks, and immediate relief after the procedure is diagnostic of the condition [20].

Infraorbital Nerve (ION) Anatomy

The maxillary nerve exits the skull through the foramen rotundum into the pterygopalatine fossa and, after giving off its other branches, passes through the infraorbital canal, emerging via the infraorbital foramen as the ION. Here, it divides into smaller branches to provide sensation to the lower eyelid, medial portion of the nose, upper teeth, and lip.

ION Block Technique

The ION block (Fig. 11.3) is done with the patient in a supine or seated position with a 25- to 30-gauge 0.75- to 1.5-inch needle. The anatomic landmark used is the infraorbital foramen, which is located approximately 5 to 8 mm inferior to the infero-orbital margin and 26 to 27 mm lateral to the facial midline. The needle is inserted just inferior to the infraorbital foramen, with care taken to not directly enter it, and contact is made with the maxilla. After negative aspiration, the injectate is placed. External manual pressure should be held at the inferior border of the orbit to prevent the spread of the injectate superiorly. Complications are similar to that of the SON block discussed above.

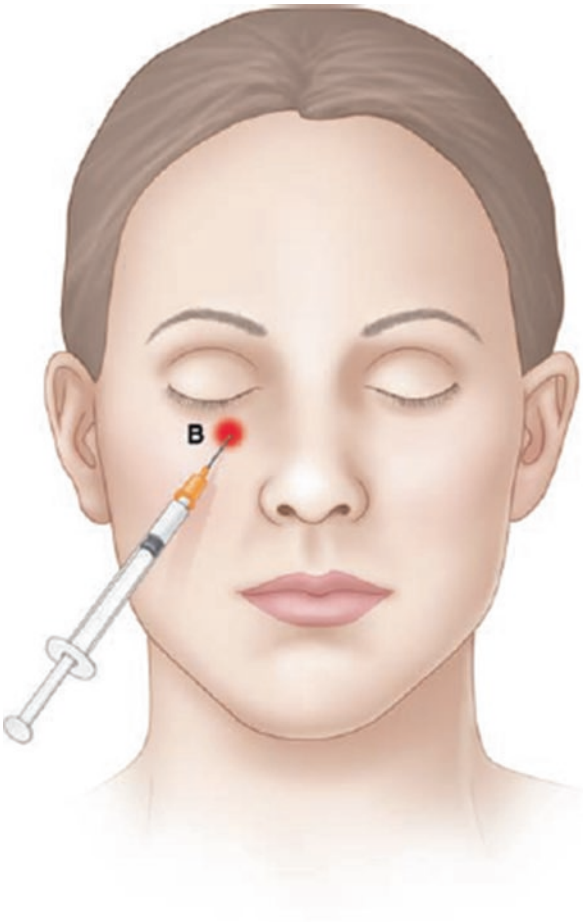

Fig. 11.3 Infraorbital nerve block

ION Treatment Evidence

Isolated infraorbital neuralgia, because it is a rare phenomenon and has similar symptoms, is often confused with trigeminal neuralgia. Infraorbital neuralgia leads to facial pain in the distribution of the ION and is amenable to blockade [21, 22]. With regard to migraine headaches, the evidence for ION block is limited to small studies. The largest study (26 patients) demonstrated that bilateral injections of local anesthetic to both the SON and ION significantly decreased the number of migraine attacks during a 6-month follow-up period [23].

Zygomaticotemporal Nerve (ZTN) and Auriculotemporal Nerve (ATN) Anatomy

The zygomatic nerve, a branch of the maxillary division, enters the orbit through the inferior orbital fissure and divides into the ZTN and zygomaticofacial nerve. The ZTN then either travels along the inferior portion of the orbit to pass through the zygomatic bone (sandwiched between the bone and temporal muscle) to enter the temporal fossa. It then pierces through the temporal fascia, at which point it sends a small branch to reach the lateral aspect of the eye, to land in and provide sensation to the anterior temple.

The mandibular division of the trigeminal nerve crosses through the foramen ovale to enter soft tissue deep to the lateral pterygoid muscle. At this point, it branches to an anterior and posterior division. The two roots of the ATN, a branch of the posterior division, surround the middle meningeal artery and then travel through the parotid gland to then branch off into six smaller branches that go on to innervate the posterior temporal region, angle of the mandible, the concha of the auricle, the external acoustic meatus, and the tympanic membrane.

ZTN and ATN Block Techniques

The ZTN block is done with the patient in a supine or seated position with a 27- to 30-gauge 1-inch needle. The anatomic landmark for this technique is the “hollow point,” an area approximately 1.5 cm lateral and 0.5 cm above the lateral palpebral commissure (along the posterior border of the zygoma) where the ZTN crosses the temporalis fascia [24]. The needle is inserted 1 cm posterolateral to and in the direction of the “hollow point” [24]. There should be an increase in resistance as the needle crosses the deep temporal fascia [25]. After negative aspiration, 0.5 to 0.75 mL of injectate is administered [24]. Complications include hematoma and infection.

The ATN block can either be performed at a distal or proximal site of entrapment. The more commonly used block targets the distal site. This block is done with the patient in a supine or sitting position with a 27- to 30-gauge needle. The distal site of injection is located by palpating for a tender area at the apex of a triangle where the base is a line connecting the tragus and the corner of the ipsilateral eye [24, 26], usually 1 to 2 cm anterior to the root of the ear helix [27, 28]. Since this area is in close proximity to the temporal artery, tenderness over the artery itself due to temporal arteritis should be ruled out [24]. The needle is inserted at this point in a cephalad direction, and after negative aspiration, no more than 1 mL of injectate is placed [24]. Complications include vascular injection, facial nerve block, infection, and hematoma.

The proximal ATN block is performed with the patient in a supine position with a 27–30 gauge needle. The injection site is located anterior to the junction of the tragus and lobule [24]. The needle is inserted superficially, and a small (0.5 mL) volume is injected [24]. Due to facial nerve proximity, there is a risk of facial nerve weakness, and the ipsilateral eye should be taped and patched if this temporal palsy occurs [24].

ZTN and ATN Treatment Evidence

Treatment for patients suspected of having ZTN- or ATN-related pain and headaches includes medications, nerve injections, neurolysis, neuromodulation, and surgical approaches. Nerve injections can be used as a starting point for diagnosis and treatment of ZTN and ATN dysfunction and can be used to guide additional treatment with neurolysis or surgery as necessary [24].

ZTN and ATN implications in headache pathology stem from their multitude of areas of entrapment. Entrapment of the ZTN can occur in the orbit near the zygomatic bone [29], as it emerges from the deep temporal fascia to become superficial [25, 30], or post-surgically [29, 31–34]. Entrapment of the ATN can occur in the infratemporal fossa due to mastication muscle spasticity or hypertrophy [35, 36], at or near the TMJ by joint inflammation or disc protrusion [35, 37, 38], or at the temple by pre-auricular fascial bands [39]. Determining that dysfunction of one nerve, and not the other, proves to be difficult given their anatomy and overlapping innervation sites.

Migraine headaches associated with the temporal region have shown to be related to dysfunction of the ZTN [25, 30, 40] and ATN [39, 41–43]. Nearly half of patients with migraine were found to have a temporal region trigger point [44].

Neurolysis with landmark-guided botulinum toxin-A injections has been described for ZTN dysfunction and associated headaches [25, 30]. Still, complications, including changes in mandibular closure motion/strength [25] and lateral rectus paralysis leading to diplopia (from presumed infiltration through the foramina of the zygomaticotemporal branch), can occur [30].

Successful treatment of ATN neuralgia has been demonstrated with local anesthetic/corticosteroid injection of the proximal branch of the nerve [45, 46]. Occasionally, patients will have ATN entrapment at both proximal and distal sites, necessitating treatment of both locations [24]. Peripheral nerve stimulation of the ATN (either alone [28, 47] or in conjunction with the GON and LON [48] has also been shown to be successful in chronic headache management.

Greater Occipital Nerve (GON), Lesser Occipital Nerve (LON), and Greater Auricular Nerve (GAN) Anatomy

The C2 spinal nerve root arises between the first and second cervical vertebra to branch into dorsal and ventral rami. The dorsal ramus goes on to give off medial and lateral branches. The lateral branch provides motor innervation to the longissimus capitis, splenius capitis, and semispinalis capitis muscles. The medial branch travels cephalad to become the greater occipital nerve (GON), providing cutaneous innervation to the medial portions of the occiput and posterior scalp. The GON travels superficially to the obliquus capitis and inferiorly/deep to the semispinalis capitis. It then pierces the semispinalis capitis and trapezius muscles near their occipital bone insertion to travel superiorly alongside the occipital artery [49].

The ventral rami of the C2 and C3 spinal roots contribute to the cervical plexus and to two cephalad traveling sensory branches, the lesser occipital nerve (LON), and greater auricular nerve (GAN). The LON courses superiorly along the posterior border of the sternocleidomastoid muscle and continues superiorly along the occiput lateral to the occipital artery [49]. The LON, also known as the smaller occipital nerve, provides cutaneous innervation to the lateral portions of the occiput scalp posterior to the ear. The GAN emerges from the posterior border of the sternocleidomastoid muscle ascending superiorly either on the anterior or posterior surface of the muscle [49]. The GAN provides cutaneous innervation to the surfaces of the ear, parotid gland, and mastoid process.

GON, LON, and GAN Block Techniques

The GON block can be performed in either the prone or sitting position with a 25- to 30-gauge 0.75- to 1.5-inch needle. The main anatomic landmarks for this technique are the occipital protuberance (inion) and the ipsilateral mastoid process of the temporal bone. There are three possible areas for injection (Fig. 11.4): 2 cm inferior and 2 cm lateral to the inion, one-third to one-half of the way lateral to midline between the inion and mastoid process, or any areas of occipital tenderness in cases of occipital neuralgia. Ultrasound may help identify and avoid the occipital artery, which tends to run lateral to the occipital nerve, but can also run medial to it. The needle is

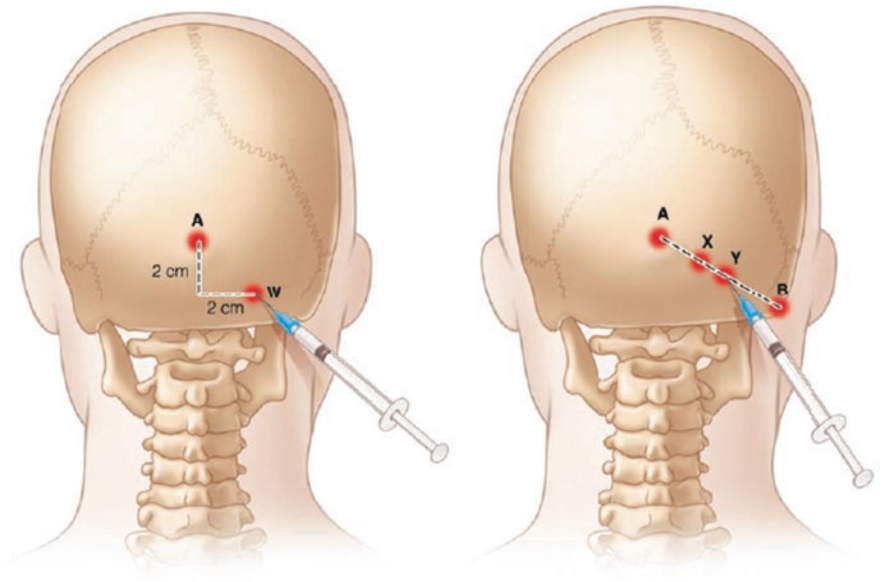

Fig. 11.4 Sites of occipital nerve block

inserted in a slightly cephalad direction until contact is made with the bone. After withdrawing slightly and confirming negative aspiration, the injectate is placed. A fanning technique may be necessary to inject in multiple areas as the location of the nerve is variable. Volumes of 1.5 to 3 mL of injectate are typically used, but there is evidence that volumes on the higher end may increase the block's efficacy [50]. An alternative technique where the nerve is targeted under ultrasound guidance in the posterior cervical spine at the level of C2 has also been described [51], but further studies into its efficacy need to be conducted. Complications include intravascular injection, hematoma, infection, hyper-/hypopigmentation of the skin due to subdermal steroid injection, alopecia, and dermal or fat atrophy.

The LON block can also be performed in either the prone or sitting position with a 25- to 30-gauge 0.75- to 1.5-inch needle. The block is performed two-thirds of the way lateral to midline between the inion and the mastoid process (Fig. 11.5). If ultrasound is used to locate the occipital artery, the LON block should be performed lateral to this vessel. The needle is inserted in a slightly cephalad direction until contact is made with the bone. After withdrawing slightly and confirming negative aspiration, 1 to 3 mL of injectate is placed. Complications are similar to those of GON block above.

The GAN block is performed in the sitting or lateral position with the affected side facing upward with a 25- to 30-gauge 0.75- to 1.5-inch needle. Ultrasound guidance is recommended due to the nerve's variable course along the sternocleidomastoid muscle. The ultrasound probe should be placed in an axial direction over the postero-inferior border of the sternocleidomastoid muscle at the level of the

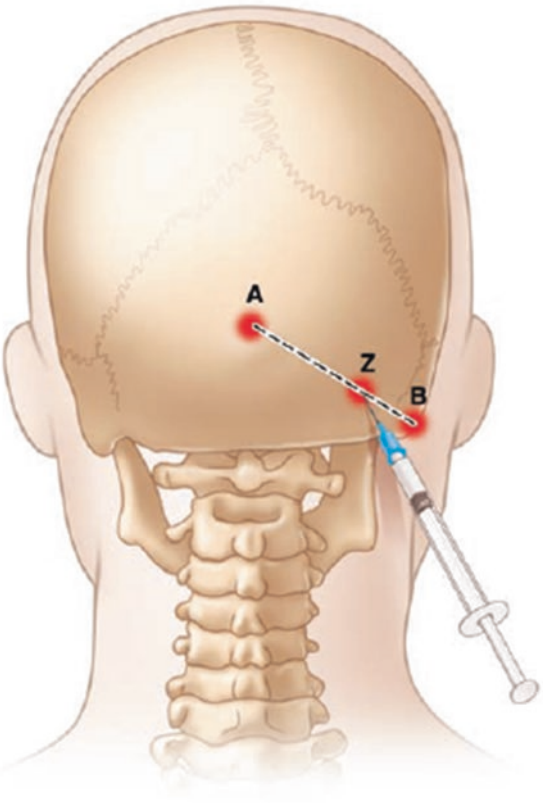

Fig. 11.5 Lesser occipital nerve block

clavicle and moved in a cephalad direction until the GAN appears either on the anterior or posterior border of the muscle, usually at the level of the cricoid cartilage. The needle is then inserted using an in-plane approach in close proximity to the nerve, making sure to avoid any vessels. Complications include intravascular injection, infection, and hematoma.

GON, LON, and GAN Treatment Evidence

The GON and LON have been targeted as a treatment for headache (in addition to the treatment of primary occipital neuralgia) due to the connection between the upper cervical nerves and the trigeminal nerves in the TCC [52], the physiology of which is further explained in the section on medial branch blocks. GON blocks have been studied as diagnostic and treatment tools in a range of headache disorders, including cluster headache (CH), migraine headache (MH), cervicogenic headache (CEH), chronic daily headache (CDH), hemicrania continua (HC), posttraumatic

headache (PTH), and postdural puncture headache (PDPH) [50]. The evidence for using the GON block is most compelling for CH, MH, and CEH [50]. As mentioned in the section above on the SON, many studies have also shown success when the SON and GON are simultaneously intervened upon.

Although the majority of studies done for GON blocks for CH treatment have been case reports or observational studies [52], the efficacy of this block has been demonstrated with a favorable safety profile. A meta-analysis for GON block in MH has shown that the intervention can significantly decrease pain intensity and analgesic medication consumption, but with no significant impact on the duration of headache [53]. With regard to CEH, studies have demonstrated the efficacy of GON block in reducing headache pain [54, 55]; however, a more appropriately targeted approach for CEH would be cervical medial branch blockade, as will be discussed later in this chapter. Some investigators have used GON blocks as diagnostic tests for cervicogenic headache, but this practice would not reliably establish a cervical source of pain since the blockade is done at a point where the nerve is too distal from the source [56].

Although to a much lesser extent, LON blocks have also been studied in patients with CH, MH, and CEH, with some promising results [57]. The greatest evidence is for CH when the LON site is tender to palpation [57]. Primary occipital neuralgia, characterized by paroxysmal stabbing pain in the distribution of the GON and/or LON, can be treated with blockade of the GON and/or LON [57, 58]. Although only limited to case reports, pulsed radiofrequency ablation of the GON has shown success in treating occipital neuralgia [59].

Isolated greater auricular neuralgia causing pain and headache in its distribution is a very rare phenomenon and usually occurs secondary to neuromas [60] or postoperatively [61]. GAN blocks for treating this condition have been efficacious [62].

Cervical Medial Branch Blocks and Ablative Techniques

Cervical Vertebrae Anatomy

Extensive knowledge of cervical spine anatomy is paramount to understanding the role cervical spine pathology plays in neck and headache pain. The relevant external anatomic landmarks of the posterior neck include the C7 spinous process, the superior nuchal line, and the greater external occipital protuberances.

The first cervical vertebra (C1), also known as the atlas, lacks a true body and, instead, has a large bony ring with lateral bony masses that articulate with the occipital bone. The union of the atlas and occiput, known as the atlanto-occipital joint, helps support the base of the skull and is active with neck flexion and extension. The second cervical vertebra (C2), also known as the axis, contains a unique central bony prominence that extends upward to sit in front of the anterior arch of C1. This structure, known as the odontoid or dens, is responsible for the majority of head and

neck rotation via its articulation with C1 (atlanto-axial joint). The atlanto-occipital and atlanto-axial joints, unlike the cervical facet (zygapophysial) joints which are innervated by medial branches of dorsal rami of cervical spine nerves, are innervated by ventral rami of C1 and C2, respectively. The medial branch of the dorsal rami of C2 travels in the cephalad direction and distally becomes the greater occipital nerve (GON), providing sensory innervation to the occiput.

The cervical vertebrae from C3 to C6 are anatomically more similar to one another. The anterior columns of these vertebrae are comprised of the anterior longitudinal ligaments, the anterior two-thirds of the annual fibrosis, and the intervertebral discs. The middle vertebral columns are comprised of the posterior one-third of the annular fibrosis and the posterior longitudinal ligaments, while the posterior columns are comprised of dorsal spinous processes, lamina, facet joints, pedicles, and transverse processes. A series of foramina transversarium allow for the vertebral artery to course superiorly from C6 to C3. The vertebral artery then travels laterally through the foramina transversarium of C2 and C1 and finally courses medially into the spinal canal. Epidural veins in the anterior and posterior epidural space vary in number according to the cervical level [63].

The cervical facet joints, which are true synovial joints, are innervated by medial branches of the primary dorsal rami of the cervical spinal nerves (Fig. 11.6). The C2/C3 facet joint follows this arrangement but is unique in its innervation. The dorsal ramus of C3 gives off two separate medial branches. The larger and more cephalad branch, also known as the third occipital nerve (TON), not only provides innervation to the C2/C3 facet joint but also provides cutaneous sensory innervation to the occiput.

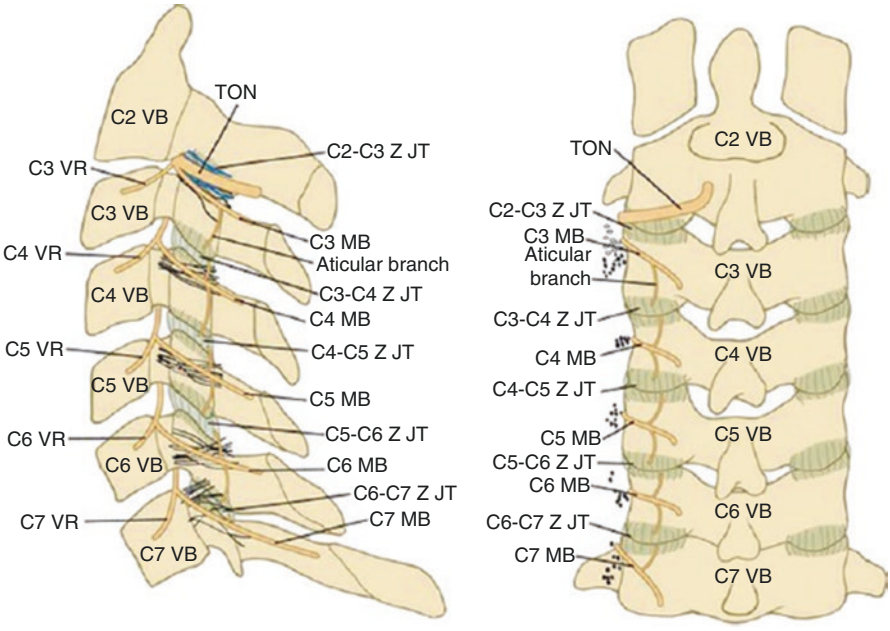

Fig. 11.6 Anatomy of cervical medial branches

The second smaller medial branch of the dorsal rami of C3 provides innervation to both the C2/C3 facet joint and the inferior C3/C4 facet joint [64, 65]. The cervical facet joints starting with C3/C4 to C7/T1 are innervated by medial branches of spinal nerves that arise from both one level above and one level below the joint. For example, the C5/C6 facet joint is innervated by both C5 and C6 medial branches. Taking this into consideration, one must anesthetize both C5 and C6 branches in order to target this joint. Lateral branches of the primary dorsal rami innervate the multifidus muscles and other muscles of the neck and provide cutaneous innervation to the overlying skin [65].

Neck Pain and Headache

The association between headache and neck pain has long been appreciated by clinicians. The anatomic connection responsible for this association was reported by Goadsby et al., who explained that cervical spinal nerves carrying pain inputs from the periphery converge with those from the trigeminal nerve onto second-order neurons in the brainstem forming a collection of cells, referred to as the *trigeminocervical complex (TCC)*. The animal-based study illustrated that stimulation of the greater occipital nerve increased metabolic activity in both the cervical region of the spinal cord and the trigeminal nucleus caudalis [1].

With regard to cervicogenic headache (CEH), this direct junction of afferent signals explains the referral patterns of cervical pain to the head. Often a headache is the presenting feature of underlying cervical spine pathology. The most common source of neck pain leading to cervicogenic headache is pathology of the upper cervical facet joints. Dysfunction of the nerves innervating the AO joint, AA joint, C2/C3 facet joint, and C3/4 facet joint may all lead to referred pain presenting as this headache type [56]. In their review of the relevant literature, Bogduk and Govind found that pain from the AA joint leads to localized pain around the occipital and suboccipital regions with referred pain to the vertex of the head, orbit, and ipsilateral ear; C2/C3 facet joint pain presents as localized pain in the occipital region with referred pain extending from the parietal region to the frontal region and orbit; and C3/C4 facet joint pain presents as pain the occipital region with referred pain to the upper and lateral cervical regions of the neck (Fig. 11.7) [56].

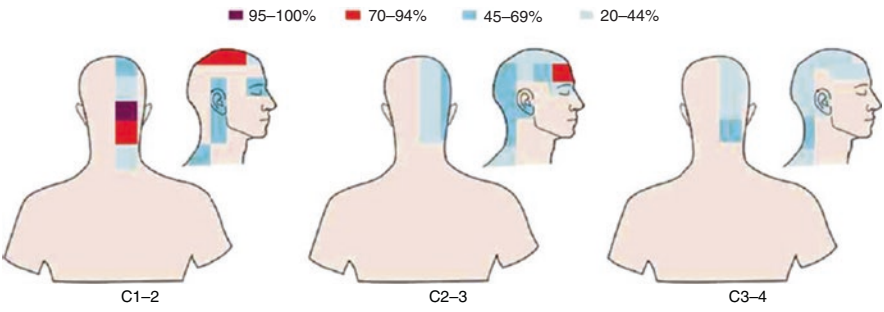

Fig. 11.7 Referral patterns of the cervical facet joints/medial branches

In addition to the direct referral of pain from the neck to the head due to possible cervical pathology, sensory input from cervical and trigeminal structures may trigger and potentiate primary headaches [66–69]. While migraine headache is generally accepted as a disease of the central nervous system, the influence of neck muscles and cervical joints on its pathology have been suspected given the high prevalence of neck pain reported by patients preceding or during an attack [70, 71]. It has been demonstrated that stimulation of cervical nerves in patients with and without a migraine diagnosis elicited head pain [72]. In addition, C1 stimulation in those patients with migraine elicited pain in a peri-orbital distribution.

An altered trigeminal nociceptive system has also been implicated in primary headache disorders. Clinical changes in the trigeminal territory, such as hyperalgesia, allodynia, and increased cutaneous sensitivity, have been seen in patients with primary headache disorders [73–75]. Chronic headache with dural inflammation may also lead to sensitization of central nociceptive neurons via trigeminal afferents and, in turn, sensitization of cervical afferents via the TCC. Bartsch and Goadsby demonstrated the link between nociceptive afferents of the dura mater and second-order neurons in the C2 dorsal horn that received input from trigeminal and cervical afferents (Fig. 11.8) [76]. One year prior, they had demonstrated that stimulation of the GON leads to central excitability of the dural afferent inputs [77], illustrating the intimate link between dural, trigeminal, and cervical afferents.

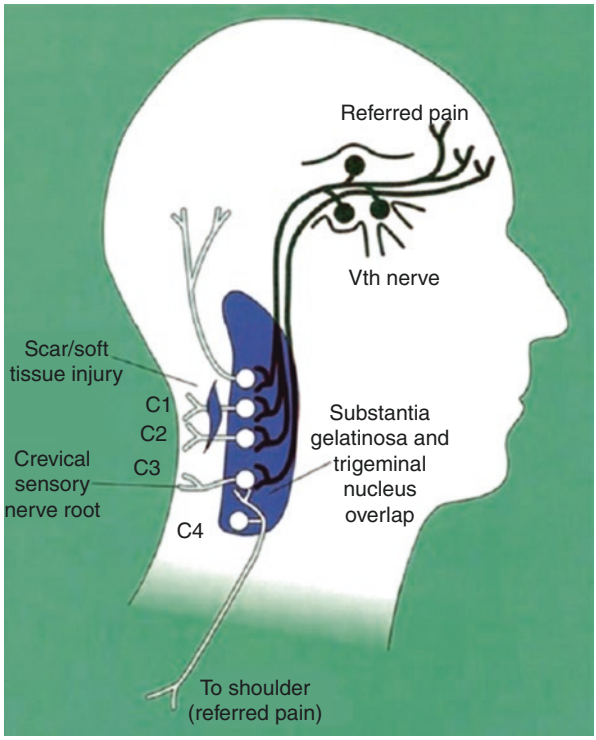

Fig. 11.8 Mechanism of cervical pain referral to the head and face and as a trigger for primary headache

This intricate link between primary headache, trigeminal afferents, and cervical afferents provides an avenue for hyperexcitability from any and all structures involved, leading to the possibility of a positive feedback loop potentiating pain in the head, face, and neck.

Cervical Medial Branch Block Technique

Cervical medial branch blocks are performed with the assistance of fluoroscopy; however, ultrasound-guided techniques have also been described. Patients are placed in either the prone or lateral position. Local anesthetic is first injected into the skin and then along the intended pathway through subcutaneous tissue and muscle to the target – the "waist" of the lateral mass of the appropriate cervical vertebra (Fig. 11.9). A 22- or 25-gauge spinal needle is then advanced, under fluoroscopic guidance, toward the target area. Local anesthetic (with or without corticosteroid) is injected after negative aspiration is done to minimize the risk of intravascular injection. Often, contrast is injected, especially at the upper cervical levels, to rule out intravascular placement. Since each cervical facet is supplied by medial branches of dorsal rami from levels cephalad to the joint and at the level of the joint, both medial branches must be anesthetized to achieve analgesia. Complications include epidural hematoma, vascular injury, intravascular injection, dural puncture, spinal cord trauma, or nerve root injury.

If significant, but temporary, relief is achieved with medial branch blocks, the nerves can be ablated with radiofrequency techniques for longer-term pain relief. However, patients will often have prolonged relief after cervical medial branch blocks, in which case these blocks may be repeated. Radiofrequency ablation (RFA)

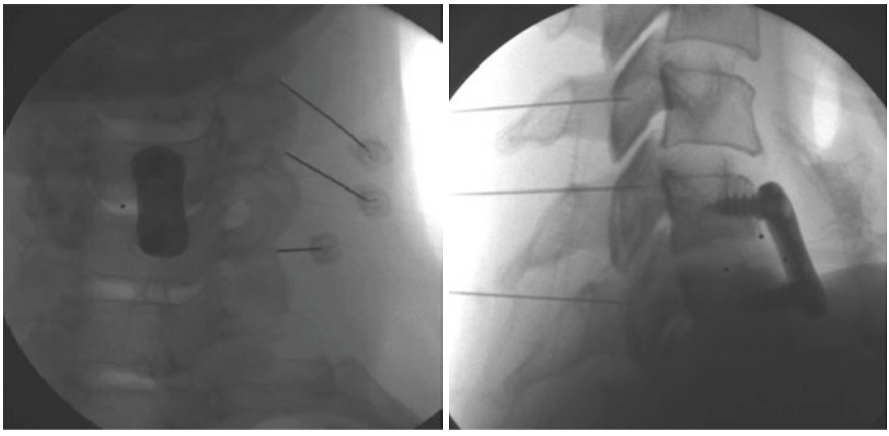

Fig. 11.9 Fluoroscopic images of medial branch blocks. Left: anteroposterior Projection. Right: lateral Projection

involves the use of electrical currents generated by an electrode active tip to produce a small area of tissue coagulation. The resultant neural ablation prevents nociceptive transmission of Aδ and C nerve fibers while leaving the medial branch nerve itself anatomically intact [78]. RFA probes are placed under fluoroscopic guidance, and low-voltage stimulation is first applied to assess for motor or sensory conduction to avoid proximity to spinal nerves. Then, either conventional (continuous) radiofrequency ablation (CRF) or pulsed radiofrequency ablation (PRF) is applied. CRF involves the administration of continuous radiofrequency current at a specific temperature (usually 80 °C) for 60 to 150 seconds leading to a neurodestructive thermal lesion [79]. PRF, the newer technique, involves the same high-frequency current as in CRF, but in brief intermittent pulses that only lead to a resultant tissue temperature of approximately 42 °C, which is below the nerve denaturation threshold of 45 °C [79]. PRF can generate a higher voltage than CRF, leading to a stronger electromagnetic field (EMF), possibly explaining the pain relief achieved without heat-induced tissue destruction [79]. This stronger EMF has been shown to upregulate neuronal transcription factors, such as c-Fos, which have been implicated in neuronal activation of a pain-inhibiting process [79]. Both CRF and PRF may be repeated if pain returns.

Medial Branch Block Evidence

The diagnosis and management of CEH ultimately depend on the resources available to the clinician. The most revealing and useful technique in diagnosis is the fluoroscopically guided block, but access to this procedure may not be available to the clinician or patient. Controlled diagnostic blocks may be performed to localize the suspected joint, and complete relief of headache after the block provides objective evidence of a cervical source of pain [56]. While some investigators have used greater occipital nerve blocks as diagnostic tests for cervicogenic headache, this practice would not reliably establish a cervical source of pain since the blockade is done at a point where the nerve is too distal from the source [56].

For a suspected AA joint source of cervicogenic headache, studies have demonstrated that the lateral aspects of the joint can be targeted with intraarticular blocks [80–82]. For a C2/C3 facet joint suspected source, the third occipital nerve can be blocked as it crosses the joint [83, 84]. For a C3/C4 facet joint and lower joints suspected source, the medial branches of the C3 and C4 dorsal rami (or the medial branches for that specific level) can be blocked [83]. For headache pain related to the C2/C3 facet joint/medial branches, the only definitively proven treatment is radiofrequency neurotomy.

It is important to note that nociceptive input from the upper cervical spine may act to trigger and potentiate primary headaches. As such, cervical medial branch blocks may be successfully employed to achieve relief not only from neck pain but from pain related to the primary headache [85].

Cervical Epidural Steroid Injection

Cervical Epidural Technique

Cervical epidural steroid injections are performed under fluoroscopic guidance, observing sterile precautions and techniques. After suspected entry into the epidural space, aspiration for blood and CSF is performed to check for intravascular or intrathecal placement. Contrast is then injected to visualize epidural spread, and the injectate is placed. Injection is typically performed at the C7/T1 interspace, as the medication will spread in the cephalad direction allowing targeting of the upper cervical levels [86]. Transforaminal cervical epidural injections have recently fallen out of favor due to the potential for complications and the lack of proven diagnostic utility of these procedures. Complications are rare but include intravascular or intrathecal injection, dural puncture with possible postdural puncture headache, spinal cord trauma, nerve injury, hematoma, and infection.

Cervical Epidural for Neck Pain and Headache Evidence

Cervical radiculitis, or cervical radicular pain in the distribution of cervical nerve roots, is pain that can be caused by compressive effects of cervical roots due to disc herniation, foraminal stenosis from degenerative or neoplastic changes, chemical effects from nucleus pulposus extravasation, acute herpes zoster or postherpetic neuralgia, or from sensitization of peripheral and central nervous system pathways. Cervical radiculopathy encompasses other more severe signs and symptoms of cervical root pathology, including weakness, sensory loss, reflex changes, or paresthesias/dysesthesias.

While there is good evidence detailing the therapeutic effects of cervical interlaminar epidural injections for radiculitis secondary to disc herniation [87], reports and evidence on the use and success of this procedure for cervicogenic headache (CEH) are limited [88–91]. Li et al. compared the effects of the combination of epidural steroid injections (ESI) and pulsed radiofrequency (PRF) of the C2 dorsal root ganglion with ESI alone [88]. A total of 139 patients diagnosed with CEH were included in the study, with 87 of them having undergone the combination of ESI and PRF and the remaining 52 having undergone ESI alone. An ESI catheter was introduced at C6-C7 intervertebral space and advanced to reach the level of C2. Both groups had significant reductions in their pain score at a 2-year follow-up. Additionally, the combination group had decreased pain scores, frequency of pain attacks, pain medications used, and inability to work compared to the ESI group.

Trigger Points

Trigger Point Anatomy

Muscular trigger points (MTrPs) are characterized by areas of distinct, palpable tenderness in taut muscle bands leading to pain in the corresponding area and referral pain to either the surrounding muscle group or to other seemingly unconnected areas. MTrPs can either be active, with passive pain at the site or latent, with pain elicited with manual palpation of the area. MTrPs are the central feature of myofascial pain syndrome, characterized by soft tissue pain in a single area of the body [92]. Underlying visceral disease, arthritic joints, joint dysfunctions, and emotional distress have been implicated as the cause for MTrPs [93]. The accepted potential biochemical cause of MTrPs is the excessive release of acetylcholine in the muscle leading to areas of local spasm, in turn, causing decreased blood flow and ischemia to the area [92]. The accumulation of lactic acid, as a by-product of anaerobic metabolism, further leads to more spasm with further ischemia. Inflammatory mediators, including calcitonin, substance-P, and tumor necrosis factor alpha, lead to nocioreceptor activation and further release of Ach, potentiating the spasm in a cyclical manner [92].

Referral Patterns

Commonly shared nociceptive neurons in the dorsal horn from the upper cervical segments and the branches of the trigeminal nerve can help explain the referral pain felt by TTH patients with trigger points in the neck, shoulder, and head muscles [94]. The proposed theory links the peripheral stimulus and sensitization of active MTrPs to possible central activation in the trigeminal nucleus caudalis, sensitizing the central nervous system [95]. This pain model proposes that the headaches experienced by such individuals are caused by referred pain elicited by the MTrPs. Headache pain, with typical features of tension-type headaches, was perceived by healthy subjects who were injected with hypertonic saline in these muscle groups (including splenius capitis, upper trapezius, and temporal muscles), supporting this concept [96] (Fig. 11.10).

Similar theories for the pathophysiology of MTrPs in MH have been proposed, with peripheral sensitization leading to TNC sensitization [97]. In MH, MTrPs have been more predominantly regarded as stimuli that may facilitate a migraine attack, rather than the primary cause [44, 98, 99]. It has been shown that patients diagnosed with TTH and MH have a larger number of MTrPs when compared to healthy subjects [98, 100–102]. With TTH, the number of MTrPs seems to correlate with the severity and duration of their headaches [103], but in MH, it does not [101]. The association between episodic and chronic tension-type headache and

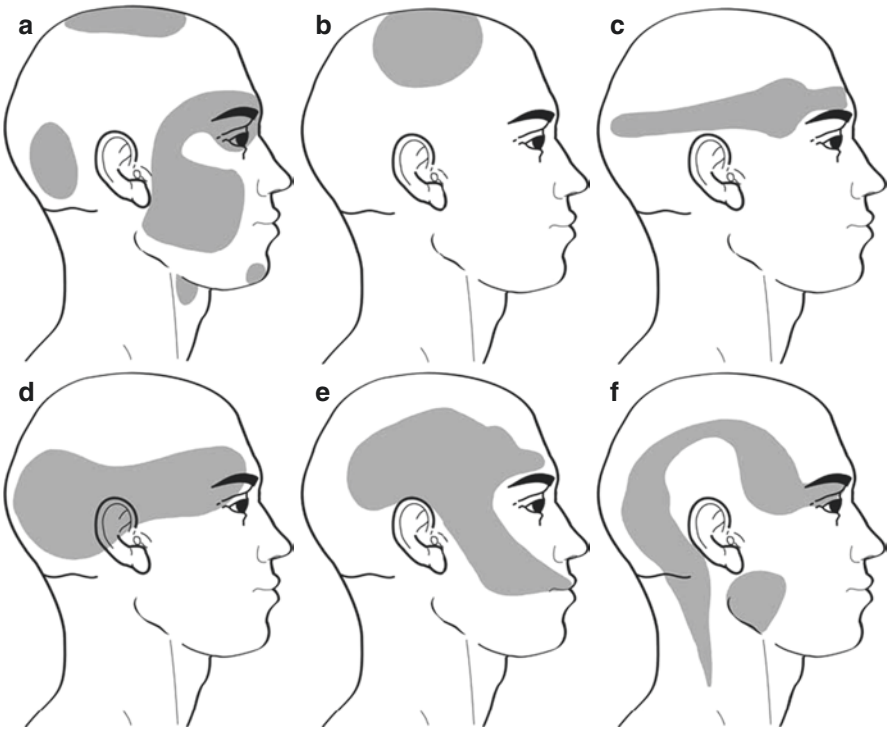

Fig. 11.10 Referral patterns of trigger points in certain muscles: (**a**) sternocleidomastoid, (**b**) splenius capitis, (**c**) semispinalis capitis, (**d**) suboccipital, (**e**) temporalis, and (**f**) upper trapezius muscles

MTrPs has been extensively studied with patients demonstrating various areas of referred pain typical of their usual headache pattern after active MTrPs were stimulated [94].

Trigger Point Injection Technique

Palpation and subsequent diagnosis of active or latent trigger points are required to accurately target and direct needle placement for successful treatment [104]. Ultrasound guidance may be used to identify specific muscles, avoid neural and vascular structures, and prevent peritoneal or pleural puncture [105]. In addition, as various "plane" blocks have gained prominence in perioperative analgesia, ultrasound use facilitates the delivery of injectate into the fascia adjacent to the affected muscles [106]. Specific complications are based on the surrounding anatomy of the MTrP being injected.

Treatment Modalities for Suspected Trigger Point–Associated Headache

Interventional treatments, including local anesthetic/steroid injections, dry needling, acupuncture, and botulinum toxin, have been proposed and attempted for targeting MTrPs given their potential role in causing tension-type headaches. Smaller studies have shown that MTrP dry needling may be as effective in decreasing headache pain as lidocaine or corticoid injections [107], and a recent randomized trial demonstrated reduced TTH intensity, frequency, and duration for dry needling over sham needling [108]. While prophylactic injections of botulinum toxin A in head and neck muscles have been shown to be effective in treating MH patients [109], no consistent effects have been demonstrated in its role in TTH, as evidenced by a systematic review [110].

Studies have demonstrated the effectiveness of local anesthetic injections into MTrPs to treat both episodic [111] and chronic variants of TTH [112], as well as MH [113]. In fact, The Peripheral Nerve Blocks and Other Interventional Procedures Special Interest Section of the American Headache Society reached a consensus on the use of bupivacaine and lidocaine in MTrPs, stating that the local anesthetics have a role in the adjunctive treatment of the most common headache disorders when employed in the appropriate setting with the proper expertise [114].

Sphenopalatine Ganglion

Sphenopalatine Ganglion Anatomy and Pathophysiology

The sphenopalatine ganglion (SPG) (also known as Meckel's ganglion, pterygopalatine ganglion, or nasal ganglion) is a small, triangular structure located within the pterygopalatine fossa (PGF). It lies inferior and medial to the maxillary nerve on the medial wall of the PGF near the lateral insertion of the posterior middle turbinate [115].

Efferent sensory branches exiting from the ganglion include the nasopalatine nerve, greater palatine nerve; lesser palatine nerve; posterior, superior, and inferior lateral nasal branches; and the pharyngeal branch of the maxillary nerve [116]. Parasympathetic fibers from the superior salivatory nucleus (SSN) synapse within the SPG, while sympathetic fibers from the superior cervical ganglion merely pass through. The parasympathetic postganglionic fibers travel with trigeminal nerve branches, providing secreto-motor function to the mucous membranes of the nose, soft palate, uvula, upper pharynx, tonsils, the roof of the mouth, upper lip and gums, lacrimal gland, and meningeal vessels [117, 118]. The sympathetic fibers passing through the SPG are distributed to the nasal mucosa, the pharyngeal mucosa, and the lacrimal gland [119]. The group of sensory, parasympathetic, and sympathetic structures in the SPG makes it the largest collection of neurons in the skull outside of the brain.

Activation of autonomic neurons in the SPG from SSN trigeminal nerve stimulation results in parasympathetic activation of the lacrimal glands, nasal and pharyngeal mucosa, and meningeal vessels [120]. This pathway, known as the trigeminal-autonomic reflex, has also been shown to cause the release of vasoactive peptides resulting in cerebral vasodilatation and neurogenic inflammation [121], ultimately leading to headache [122]. The headache and autonomic symptoms of trigeminal autonomic cephalalgias (TACs) mimic the activation of the SPG, suggesting that the SPG can be targeted therapeutically to treat these disorders [123], as well as numerous other headache disorders. The effectiveness of SPG blockade in migraine has been attributed to the autonomic symptoms often present in this condition [120]. Other headache disorders amenable to SPG blockade include trigeminal neuralgia, posttraumatic headache, sphenopalatine neuralgia, and atypical facial pain [124]. Also, recent evidence has emerged that SPG blockade can be used as an alternative to epidural blood patch in treating postdural puncture headache [125].

SPG Block Techniques

Methods of SPG blockade include transnasal, transoral, and lateral application of local anesthetics. Commercial devices for transnasal application have recently been developed. More invasive techniques for targeting the SPG include radiofrequency ablation (RFA) and neurolysis.

The transnasal approach involves placing pledgets soaked in local anesthetic through the nares until contact is made with the posterior border of the middle turbinate (Fig. 11.11). The pledgets are left in place for 20 to 30 minutes while the patient remains in a supine position [126]. Alternatively, local anesthetic may be

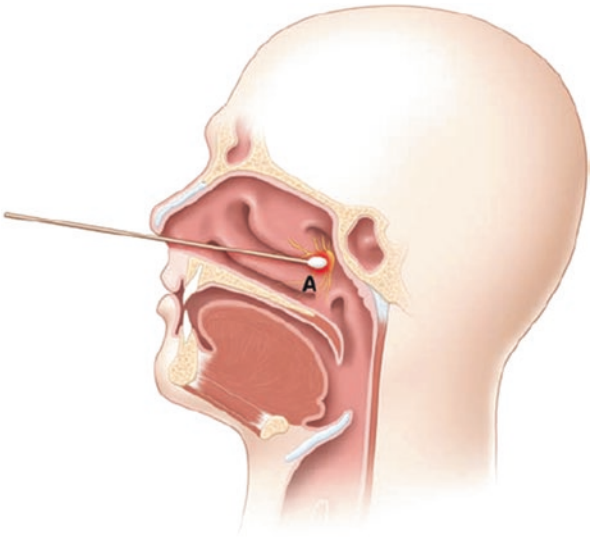

Fig. 11.11 Sphenopalatine ganglion block: transnasal approach

delivered via a catheter. Commercial devices for transnasal application include the MultiGuide® (Trondheim, Norway), Tx360®, SphenoCathVR, and AllevioVR SPG. The main risk for this technique is epistaxis.

The transoral approach involves placing the patient in a supine position with their mouth maximally open. The landmark for this technique is the greater palatine foramen, which is located medial to the second or third molar. A 25- to 30-gauge 1.5-inch needle (with a bend) is placed through this foramen while aiming in the cephalad and posterior direction. After negative aspiration for blood, 1 to 2 mL of local anesthetic is then injected. The risk of this technique includes pain on injection or paresthesia if contact with the greater palatine nerve within the foramen is made.

The lateral approach also involves having the patient in a supine position and is similar to the lateral coronoid approach for trigeminal ganglion block. The coronoid process of the mandible is first palpated, and a 22- or 25-gauge needle is inserted cephalad in a lateral to medial direction aiming toward the sphenopalatine fossa. Under fluoroscopic guidance, the needle is directed toward the sphenopalatine fossa until the palatine bone is contacted. A lateral image is then taken to confirm the location, and a local anesthetic is subsequently injected. Risks for this technique include hematoma and inadvertent trigeminal ganglion block due to its proximity.

SPG Block Evidence

SPG Blockade and Cluster Headache

The earliest reported intervention on the SPG to treat headaches (likely of the cluster headache (CH) variety) was demonstrated in 1908 when Sluder blocked the SPG via a transnasal approach with cocaine in concentrations of 4, 10, and 20% [127]. The largest SPG blockade study was done in 1981 by Devoghel, where he described successful treatment of CH and parasympathetic symptoms using alcohol infiltration via the suprazygomatic approach. The study reported that 103/120 (85.8%) of patients had resolution of their pain and symptoms, with 16 of them remaining pain-free for 1–2 years, 17 remaining pain-free for 2–3 years, and an additional eight remaining pain-free for 3 years or more [128].

A double-blind, placebo-controlled trial examined the effects of 10% cocaine hydrochloride, 10% lidocaine, and saline administration as abortive treatments for nitroglycerin-induced cluster headache [129]. The medications were administered transnasally and bilaterally via cotton swab to 15 patients under anterior rhinoscopy guidance, and all patients had relief within minutes, with no significant difference found between cocaine and lidocaine. Those receiving saline did not have effective results. An open-label, uncontrolled pilot study investigated the administration of onabotulinumtoxinA (BTA) injection into the SPG using the MultiGuide® device and surgical navigation for intractable CH under general anesthesia, with the authors reporting a reduction in patients' CH attack frequency.

While these studies have demonstrated the efficacy of local anesthetic and alcohol application in treating CH, the results show more of an abortive role with less permanent relief typically achieved. Patients demonstrating success with these less invasive techniques may benefit from longer-lasting options such as radiofrequency ablation (RFA). In the largest study of SPG RFA, 66 patients with intractable CH (with 56 suffering from episodic CH and 10 suffering from chronic CH) were treated with radiofrequency lesioning of the SPG via the infrazygomatic approach [130]. Over a 12- to 70-month follow-up period, 61.7% (34/56) of those with episodic CH reported complete relief of pain, while 30% (3/10) of those with chronic CH had complete relief of pain. While these results better demonstrate the efficacy of RFA on episodic CH, chronic CH has also been reported to be successfully treated in long-term (24 months) follow-up [131]. In a study done with percutaneous RFA via infrazygomatic approach in 15 patients with chronic CH who previously experienced temporary relief with SPG block, 46.7% (7/15) reported a change in their CH from chronic to episodic form and were able to cut down on their preventative medications.

Pulsed radiofrequency (PRF) is yet another option available for targeting the SPG, with multiple studies reporting its success and safety in CH treatment [132–134]. The largest of these studies evaluated CT-guided PRF treatment of the SPG in 16 CH patients who had not responded to conservative management with 84.6% (11/13) of episodic CH patients and 33.3% (1/3) of chronic CH patients reporting complete relief of symptoms at the mean follow-up time of 17 months.

SPG Blockade and Migraine

The role of SPG blockade with transnasal lidocaine for the treatment of MH has been reported in numerous studies [135–139], with controlled studies yielding mixed results overall. In a placebo-controlled study published in 1996 [138], 81 patients with MH were treated with either 4% transnasal lidocaine or saline. Those treated with lidocaine were significantly more likely to experience relief from their MH symptoms (e.g., headache, nausea, and photophobia) within 15 minutes than those treated with saline, but many patients had a recurrence of their headache within 1 hour of treatment. In 1999, a randomized, controlled, double-blinded study investigated the use of self-administered 4% transnasal lidocaine on 131 patients, with lidocaine found to be superior to placebo in aborting MH [137]. However, recurrence of symptoms was once again an issue, with 21% of those receiving lidocaine having relapse of their headache. In a randomized controlled study conducted in the emergency department, no significant difference in pain reduction was found between patients receiving 4% lidocaine or placebo [135]. In more recent years, researchers have attempted to utilize devices, including the Tx360® and MultiGuide® (Trondheim, Norway), to guide various SPG-targeted therapies for MH. In a double-blind, placebo-controlled study at two headache centers in the USA, the Tx360® device was used to transnasally inject the SPG with either 0.5% bupivacaine or

saline for 6 weeks, with twice-weekly injections [140]. A total of 38 patients were included, with 26 receiving bupivacaine and 12 receiving saline. Those receiving bupivacaine reported statistically significant reductions in pain scores at baseline, 15-minute, 30-minute, and 24-hour intervals. Those receiving saline also reported statistically significant reduced pain scores at 15-minute and 30-minute intervals but had statistically significant increased pain scores at the 24-hour interval. While not statistically significant, the repeated SPB blockade did lead to an overall decreasing trend in MH pain during the 6-week study period. In an open-label uncontrolled study with a 12-week follow-up, the MultiGuide® device surgical navigation was utilized to inject onabotulinumtoxinA (BTA) bilaterally into the SPG in 10 patients suffering from chronic intractable MH [141]; 80% (8/10) patients reported at least a 50% reduction in the number of their moderate and severe headache days as compared to baseline and second-month post-treatment. The most commonly experienced adverse effects cited were localized edema and pain at the injection sites, which resolved by the conclusion of the study.

SPG Blockade and Other Headache Disorders

Postdural puncture headache (PDPH), the most common serious complication occurring from lumbar punctures and epidural/spinal anesthetics, can be a debilitating and even life-threatening occurrence [142]. The gold standard for the treatment of severe PDPH is the epidural blood patch (EBP) [143]; however, SPG blocks have been investigated, as well. A retrospective review at one institution of patients who had undergone intervention for PDPH reported a greater number of patients showing quicker onset of significant relief with SPG blockade compared to EBP, with no complications encountered with the blockade [125].

Stellate Ganglion

Stellate Ganglion Anatomy

The stellate ganglion (SG) (cervicothoracic ganglion) is an irregularly shaped structure formed by the fusion of the seventh cervical and first thoracic sympathetic ganglions. This structure, which is present in approximately 80% of the population, lies anterior to the neck of the first rib (extending to the inferior aspect of the transverse process of C7) and anterolateral to the longus colli muscle. The SG is posteromedial to the vertebral artery, posterior to the common carotid (near the subclavian artery branch point) and internal jugular vein, and medial to the superior intercostal artery [144]. The SG lies posterior to the phrenic nerve and dome of the pleura and is bound medially by the vertebral column, esophagus, and trachea. Efferent nerves emerging from the SG include gray rami communicantes to the seventh, eighth, and first thoracic spinal nerves, cardiac and vagus nerve branches, and branches to surrounding blood vessels. The blood vessel branches join to form plexuses on the subclavian artery and its subsequent branches [145, 146].

SG Blockade Technique

SG block is done with the patient in the supine position with their head extended under fluoroscopic guidance. CT scan, MRI, or ultrasound can also be used. The main palpable anatomic landmark is the anterior tubercle of C6 (Chassaignac tubercle), which lies against the cricoid cartilage. The target area is typically the anterior junction of the transverse process and the vertebral body of C6 (or C7). A successful block will elicit temperature changes in the ipsilateral upper extremity and will typically result in a temporary Horner's. Complications include vascular injury, brachial plexus injury/block, thyroid trauma, tracheal trauma, pneumothorax, and spinal/epidural injection.

SG Blockade Evidence

Most commonly, SG blockade is used to treat complex regional pain syndrome of the upper extremities. Large placebo-controlled, double-blinded studies have not been performed with those blockades, but reports have demonstrated their utility in the treatment of some forms of headache [147–151], including cluster headache (CH) [147], headache following internal carotid artery dissection [150, 151], and posttraumatic headache [148].

SG blocks, performed in ten patients diagnosed with CH, resulted in 80% (8/10) of the patients experiencing abortion of the headache. The other one or two patient case reports have published promising results for SG blockade in sympathetically mediated pain in the orofacial region [152], head and neck cancer pain [153], and temporal arteritis [154–156]. Although the mechanism for headache relief from SG blockade has not been fully clarified, it is theorized that stabilization of the abnormal sympathetic nerve function and suppression of inflammation of the vascular wall is responsible [149].

Temporomandibular Joint Disorders/Dysfunction (TMD)

Temporomandibular Joint Anatomy

The temporomandibular joint (TMJ), in coordination with the muscles of mastication, neck muscles, and hyoid muscles, allows for protrusion, retraction, elevation, and depression of the mandible. The TMJ, as its name suggests, consists of articulations between the head of the mandible and the temporal bone. More specifically, the mandibular head articulates with both the mandibular fossa and articular tubercle portions of the temporal bone (Fig. 11.12). It is considered a diarthrosis/synovial joint whose articulation allows for free movement within the joint space. The joint structure is composed of a synovial cavity and articular cartilage surrounded by a capsule. Three extracapsular ligaments (lateral, sphenomandibular, and

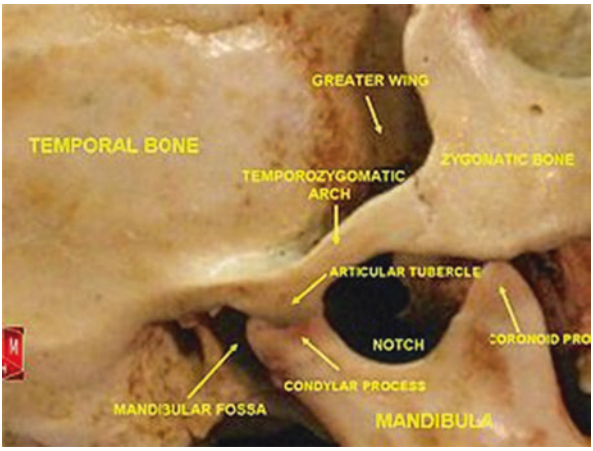

Fig. 11.12 Anatomy of the TMJ

stylomandibular) help to stabilize the joint. Arterial supply to the TMJ is provided principally by the superficial branch of the external carotid, while innervation to the joint is provided by the *auriculotemporal* and masseteric branches of the mandibular nerve.

Temporomandibular Dysfunction and Headache

Temporomandibular dysfunction (TMD), according to the American Academy of Orofacial Pain, is defined as a clinical problem involving the TMJ, masticatory muscles, and other related structures [157]. Signs and symptoms include pain in the face, jaw, head, or ear, limitations in masticatory function, deviation of the mandible, and noises ("clicking," "popping," or "grinding") of related structures.

Clinicians must be knowledgeable about the association between TMD and headache, particularly migraine, given the common co-occurrence of both pathologies. The International Headache Society has recognized that secondary headaches can be attributed to TMD [158], and large population studies have demonstrated the relationship [159–162]. It has been shown that women with migraine are more likely also to have TMD compared to women without headache [163]. Additionally, a dose relationship has been shown to exist between headache and TMD [160]: the higher the frequency of headaches in general, the higher the number of TMD symptoms. Likewise, the higher the number of TMD symptoms, the higher the frequency of headaches. Given this information, it can be reasoned that either TMD favors the onset of headaches, or conversely, headaches favor the onset of TMD [164].

TMJ Block Technique

The TMJ may be blocked either under CT, ultrasound, or fluoroscopic guidance. The fluoroscopic approach involves positioning the patient in a lateral position with the head tilted toward the table. This positioning allows separation of the otherwise overlapping left and right TMJ joints, with the dependent (down) joint appearing as inferior on the fluoroscopic image and the non-dependent joint (up) appearing as superior. After anesthetizing the skin, a 25G needle is directed into the joint to contact the superior aspect of the mandibular head. A small amount of contrast is administered (Fig. 11.13) to confirm intra-articular position, and then the injectate, usually a combination of local anesthetic/steroid, is administered.

TMD Treatment Evidence

Understanding the correlation between TMD and headache, especially migraine, aids the clinician in pursuing treatment options that will benefit the patient. Reports have shown that better migraine outcomes are achieved for patients when their comorbid TMD is also treated [165]. Botulinum toxin-A injections into the temporalis muscles [166] and/or masseter muscles [166, 167] in patients with comorbid TMD and tension headache can help reduce TMD symptoms [166, 167], headache pain [166, 167], and the number of headache days [166, 167]. Injections of glucocorticoids and/or hyaluronic acid, as well as platelet-rich plasma (PRP) for TMD, are safe and effective, with very few reported side effects [168–180].

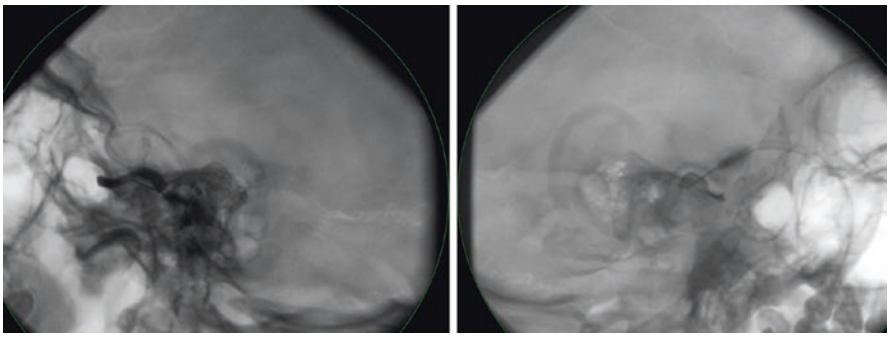

Fig. 11.13 Fluoroscopic image of TMJ injections with contrast outlining joints. Left panel: bilateral TMJ injections. Right panel: right TMJ injection (Source: Private image library of Yury Khelemsky, MD)

Spontaneous Intracranial Hypotension

Spontaneous Intracranial Hypotension Anatomy

Spontaneous intracranial hypotension (SIH), also known as craniospinal hypovolemia or spontaneous cerebrospinal fluid (CSF) hypovolemia, is an important cause of secondary headaches typically caused by CSF leaks [181]. The symptoms most commonly encountered and included in the diagnosis of SIH are orthostatic headache, neck and interscapular pain, cochleovestibular manifestations, and cranial nerve palsies [182]. The diagnosis of this condition has dramatically increased in recent years due to increasing awareness and a better understanding of the underlying pathophysiology involved.

Fragile meningeal diverticula leading to spontaneous CSF leaks were some of the earliest recognized causes of SIH [183, 184]. Normal perispinal cystic structures and Tarlov cysts may mimic these diverticula [185, 186], however, and as a result, diagnosis of SIH in patients with incidental findings of benign cysts becomes complicated. Recently, evidence has emerged for other possible causes, including ventral dural tears [187] and CSF-venous fistulas (Fig. 11.14) [188, 189]. In one study of 568 patients with SIH, ventral dural tears were found in approximately 25% of cases [187]. Since CSF-venous fistulas lead to loss of spinal fluid into the circulatory system and not the epidural space, their detection on conventional spinal imaging is difficult [190]. Digital subtraction myelography, however, has shown promise in the detection of these abnormal connections in SIH patients [191, 192], especially when performed in the lateral decubitus position [193].

Classically, low CSF pressure, orthostatic/positional headaches, and characteristic imaging findings were the hallmarks of SIH owing to the understanding that spinal CSF leaks conventionally manifest as these signs and symptoms [190]. However, large studies have reported that the incidence of low opening pressure is

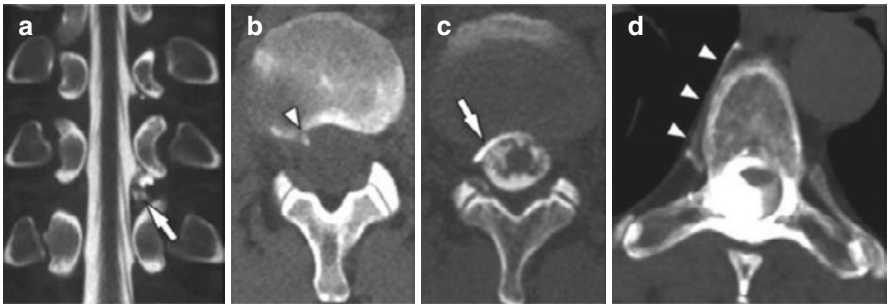

Fig. 11.14 Various causes of CSF leak in SIH illustrated by CT myelography. (**a**) Coronal image shows contrast leakage (arrow) inferior to an irregular nerve root diverticulum. Axial CTM image from before (**b**) and after (**c**) intrathecal contrast injection shows a sharp osteophyte (arrowhead) causing a CSF leak (arrow). (**d**) Axial CTM image shows myelographic contrast filling a paraspinal vein (arrowheads), indicating the presence of a CSF-venous fistula [188]

not as widespread as previously thought, with only 21–55% of patients with SIH exhibiting this sign [194–196]. With regard to headache, studies have shown that not only do a fair amount (23%) of patients diagnosed with SIH lack the typical orthostatic headache [197], some (although uncommonly) may lack a headache altogether [198]. The most characteristic and specific finding reported on imaging is the presence of diffuse dural enhancement [199, 200]. Other findings that have been reported include hyperemia of the pituitary gland, sagging of the midbrain, and engorgement of dural venous sinuses [184]. However, a study reporting the incidence of imaging findings in confirmed SIH patients questions the sensitivity of these findings in making a diagnosis. Dural enhancement, brain sagging, and venous distension were only present in 83%, 61%, and 75% of patients, respectively [201]. Due to the lack of a single diagnostic test sensitive enough to definitively make the diagnosis, a combination of multiple imaging and procedural modalities, including brain/spine imaging and CSF pressure measurement, may need to be pursued in a comprehensive assessment of patients with suspected SIH [190].

Epidural Blood Patch in SIH

The commonly accepted first-line treatment for patients with SIH is the epidural blood patch (EBP). This procedure involves the injection of autologous blood into the epidural space through a needle or catheter. Conventionally used in the treatment of postdural puncture headaches (PDPHs) where a known procedure has typically led to a disruption of the dura, the epidural blood patch is utilized in SIH with the intent of sealing a presumed or known dural defect causing a CSF leak (Fig. 11.15).

Patients with diagnosed PDPH typically achieve rapid improvement in their symptoms once an EPB is performed. Rarely, a PDPH patient will require multiple

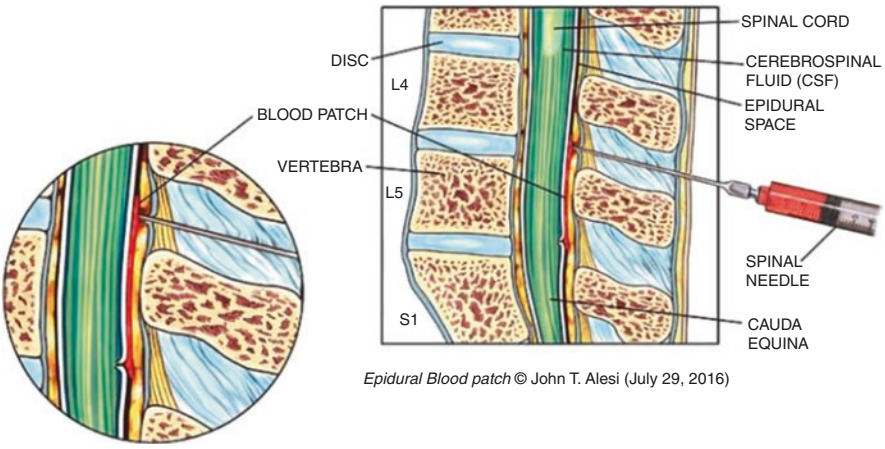

Fig. 11.15 Epidural blood patch

EBPs for successful treatment. The diagnosis of PDPH is usually made quickly because of the known inciting event, and subsequent prompt treatment with an EBP can mitigate chronic changes to the central nervous system. Misdiagnosis is common in SIH however, leading to a delay in effective treatment [202]. Dilation of intracranial and paraspinal veins, as well as sensitization of the dura mater and central neural structures and triggering of primary headache disorders, may then have time to develop [203]. These chronic changes rarely improve immediately after a blood patch, and multiple EBPs may be necessary for symptom remission [190].

Epidural blood patching can either be done "blind" (non-targeted) or targeted, in which the proceduralist uses previously done imaging to localize potential site(s) of CSF leak amenable to patching. Non-targeted patching is traditionally done at the lumbar region, is less technically complex, and is usually done when the site of the CSF leak is not known. The imaging modalities that are typically used to localize a CSF leak and guide the targeted approach include CT myelography, dynamic (or ultrafast) CT myelography, dynamic myelography under conventional fluoroscopy (with or without digital subtraction), and MR myelography with intrathecal gadolinium [204]. Non-targeted patches can be performed with or without image guidance.

Reports have shown varying success rates for initial non-targeted EBPs in SIH, with studies citing the resolution of symptoms after the first treatment in the range of 30–70% [205–208]. Recent studies have emerged attempting to identify procedural predictors of first EBP efficacy [209]. A large cohort of patients [202] receiving a total of 604 EBPs was retrospectively studied with analysis showing that the volume of blood injected, the initial number of levels injected, and site-directed strategies (targeted EBPs) significantly correlated with a higher likelihood of success after first EBP [209]. This study also found that in cases with confirmed SIH, the presence of acute angles of sag on MRI (midbrain-pons angle <47° and/or vein of Galen/straight sinus angle <58°) or at least four brain SIH MRI abnormalities (pachymeningeal enhancement, brain sag, pituitary enlargement, subdural fluid accumulation, or venous engorgement) predicted a negative response to first EBP [209]. The authors postulated that in cases with these negative prognostic indicators, early invasive testing to localize the CSF leak site to guide a targeted approach may be beneficial [209].

If a CSF leak site is known or highly suspected, targeted EBP can be utilized, and reports have demonstrated an increased success rate over a non-targeted technique [207, 208]. The larger of these studies found that 87% of patients receiving targeted EBP exhibited clinical improvement after first administration, compared to only 52% of patients receiving non-targeted patches [208]. With targeted EBPs, fibrin sealant can be also be used to help promote closure of the dural defect since the procedure is done at the level of the known leak [210].

The use of real-time image-guided EBP has recently emerged as an alternative technique to traditional anatomically guided approaches. The two imaging modalities that have been most investigated include CT and fluoroscopy. The literature for CT-guided EBP is still developing with mostly case reports with few complications reported [211–216]. One study reported on a cohort of 8 patients with SIH evidence on prior imaging who underwent CT-guided myelography followed by immediate CT-guided blood patching [217] and post-treatment imaging. Their investigation

found that all patients demonstrated both subjective improvements in their symptoms and objective reversal of SIH-associated image findings. Total CT fluoroscopy time for the initial procedures averaged 45 seconds, with a range of 18–72 seconds.

The largest overall study done on CT-guided EBP for SIH examined the role of ventral epidural space targeting in 25 patients who had undergone a total of 72 procedures [218]. Patients included in this study had radiologic evidence of CSF leak arising from the ventral dural surface, and most had at least one prior conventional EBP. The study reported that 95.8% of needle placements were technically successful, but inadvertent intravascular injection was identified in 29.3% of these, necessitating needle repositioning. The authors stated that these were all "considered venous," but only 9 of the 22 intravascular placements were "definitely venous." Successful resolution of symptoms was achieved in 41% of patches, leading to patient relief for at least 2 months. While a high technical success rate was achieved, the high rate of intravascular placement and moderately low rate of success illustrate that this technique should be reserved for those with confirmed ventral CSF leaks refractory to conventional EBP methods.

EBP for SIH done under fluoroscopy appear to be safe and effective [219–222]. This technique has the benefit of image guidance (and contrast verification) with much shorter procedure times (patient comfort) and less radiation exposure than CT-guided spine procedures [223]. Furthermore, placement of a guidable epidural catheter via an epidural needle under live fluoroscopic guidance allows for targeting of multiple spinal segments with a single epidural entry [224]. This is significant, as each epidural needle placement during a multi-level patch increases the risk of a dural puncture. Furthermore, a catheter-based technique allows entry into the epidural space distal from higher risk areas (i.e., cervical spine and location of previous spinal surgery) and advancement of the catheter to the target area [225]. Figure 11.16 depicts a cervical epidural blood patch at C5/6 performed by inserting a guidable catheter via an epidural needle positioned in the T1/2 interlaminar space.

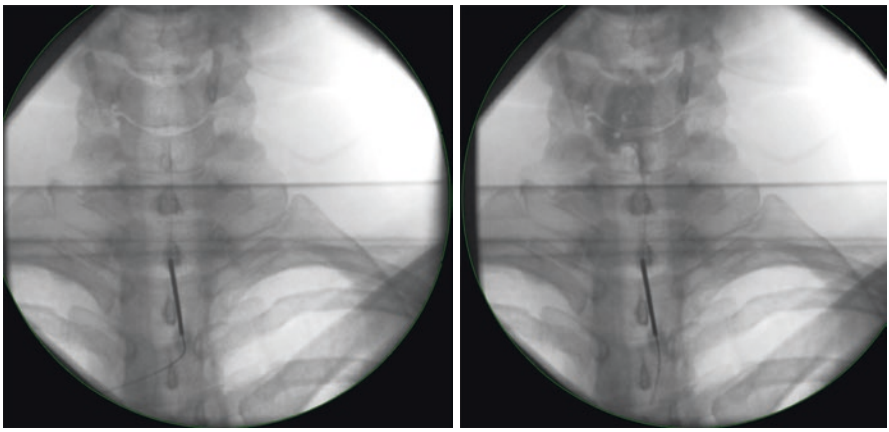

Fig. 11.16 Cervical epidural blood patch. Left panel: epidural needle in T1/T2 interlaminar space with catheter advanced to the level of C5. Right panel: contrast dye injected via the catheter demonstrates spread at C5/6

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Chapter 12
Surgical Interventions

Richard Ogbuji and Brian Harris Kopell

Introduction

The management of frequent headaches primarily employs a number of effective pharmacologic and non-pharmacologic therapies. Tricyclic antidepressants, topiramate, valproic acid, onabotulinumtoxinA injections, CGRP monoclonal antibodies, as well as cognitive behavioral therapy and biofeedback therapies, among others, are all part of the standard armamentarium of headache management [1]. There exists, however, a substantial population of patients for whom these first-line therapies are not satisfactory. Refractory chronic migraine, for example, affects approximately 4% of the population worldwide [2, 3] or up to one-third of all migraine sufferers [4].

Surgical therapies for refractory headache, the focus of this chapter, can be broadly categorized into two groups: ablative or neurostimulatory. Neurostimulation relates to various treatment modalities employing electrical stimulation directly or indirectly, to peripheral nerves or to brain parenchyma itself. Among the multiple modalities of neurostimulation, occipital nerve stimulation, transcutaneous supraorbital nerve stimulation, sphenopalatine ganglion stimulation, deep brain stimulation, and transcranial magnetic stimulation are discussed. Ablative techniques discussed will include supraorbital nerve decompression, glycerol and radiofrequency rhizotomy, and gamma knife radiosurgery. Microvascular decompression surgery, which does not neatly fall into an "ablative" or "stimulatory" heading, are also discussed.

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History

The field of neurostimulation for headache has evolved over the past several decades. In 1999, the work of Weiner and colleagues [5] demonstrated, for the first time, the successful application of subcutaneous electrostimulation for intractable occipital neuralgia. Later work by Popeney went on to demonstrate a significant reduction in migraine headaches with C1 through C3 peripheral nerve stimulation [6]. The pathophysiology of headache (chronic migraine and cluster headache) was further elucidated with positron emission tomography (PET) imaging work done by Weiller [7] and May [8]. Several areas of the brain associated with pain, including the cingulate and frontal cortex, insula, basal ganglia, and cerebellum, were found to be activated during headache. The activation of specific brain regions during headache was further examined in chronic migraine patients undergoing occipital nerve stimulation. In 2004, the work of Matharu demonstrated that significant changes in regional cerebral blood flow (rCBF) in the dorsal rostral pons, anterior cingulate cortex (ACC), and cuneus correlated to pain scores [9]. Following the 1999 investigation by Weiner, the field of peripheral nerve stimulation (PNS) for headache evolved along two paths: PNS for cephalalgia and PNS for primary headache.

Neuropathic syndromes, including occipital neuralgia, cervicogenic headache, other intractable C2-mediated headaches, and supraorbital neuralgia, have all found high levels of success with PNS, with between 70% and 100% satisfactory response rates reported in the literature [10]. In 2003, the first reports of PNS for primary headache by Dodick described a positive response to occipital nerve stimulation (ONS) in a patient with cluster headaches, and Popeney found similar results in a series of patients with transformed migraine [10]. Multiple studies followed the Dodick 2003 publication, and on average, reported a 62% response rate to PNS for primary headache conditions.

Surgical interventions targeting trigeminal neuralgia have their roots with the pioneering work of Dandy, who was among the first to successfully describe his series of over 200 patients treated with transection of the trigeminal nerve root via retromastoid craniectomy. Later, in the 1950s, Taarnhoj, Gardner, and Miklos adopted an extended subtemporal approach and described "non-traumatic manipulation" of the sensory root. Jannetta later went on to refine the technique and popularized both the retrosigmoid approach and the theory of vascular compression as the cause of TN in the 1960s [56].

Occipital Nerve Stimulation

Pathophysiology

The precise mechanism by which occipital nerve stimulation works to alleviate headache is not fully understood. The greater, lesser, and third occipital nerves provide sensory innervation to the occiput. Nociceptive fibers project to the upper

cervical spine dorsal horns that are continuous with the trigeminal nucleus caudalis. Thus, C1, C2, and C3 dorsal horns and the trigeminal nucleus caudalis form the trigeminocervical complex (TCC). This complex then transmits nociceptive information to higher centers in the brain. Depolarization of the occipital nerves, resulting in anterograde impulse propagation, may serve to modulate both central and peripheral nociception targets. Electrical stimulation has been shown to alter conduction velocity in A-delta nociceptive fibers and change the excitability of the nerve itself in animal models, which may be one method of pain reduction [11]. Current indications include occipital neuralgia, chronic daily occipitally mediated migraine headache, intermittent migraine headache with occipital triggers, chronic neuropathic pain in an occipital distribution, and cervicogenic occipital pain.

Technique

The procedure is usually staged, with trial stimulation performed over several days to determine the effect. If successful, a second procedure is then done with a permanent implant of the programmable pulse generator. The stimulator implant for occipital nerve stimulation can be performed from either a midline or lateral approach. Ultimately, the stimulator must be placed at the level of the occipital-cervical junction in the subcutaneous fat and parameters of pulse width, frequency, and amplitude adjusted until slight paresthesia in the distribution of the occipital nerves is noted. As described by Weiner and Reid originally in 1999, a lateral incision near the mastoid process is made with the lead implant directed toward the midline at the level of C1 [5]. Kapural described the midline approach in 2005 [13]. The midline approach is generally preferred today for several reasons. First, the amount of subcutaneous fat is greater at the midline, allowing the surgeon to make a large enough subcutaneous pocket for the lead and strain relief loop. Second, the location of the incision mitigates patient complaints with regard to pain if wearing glasses or other items near the ear. Third, from one midline incision, electrodes can be placed bilaterally [11]. Occipital nerve stimulation electrodes are typically the same electrodes that are used for spinal cord stimulation and are manufactured in either a paddle or cylindrical configuration. There is evidence that paddle-type electrodes, which require more surgical dissection, result in less scar tissue formation, and a better stimulation field with less chance of migration [14].

Patients may be positioned prone, lateral, or supine with the head turned. Prone positioning usually results in placing the implantable pulse generator (IPG) near the upper buttock, with lead tunneling then being done over a relatively long distance. While technically feasible, this positioning poses a greater risk for lead migration due to excessive stretch with forward bending at the mobile upper cervical region postoperatively. Lead migration rates have been reported as high as 24% of implants [21]. Either the supine or lateral position allows for IPG implantation in the upper chest below the clavicle (Fig. 12.1).

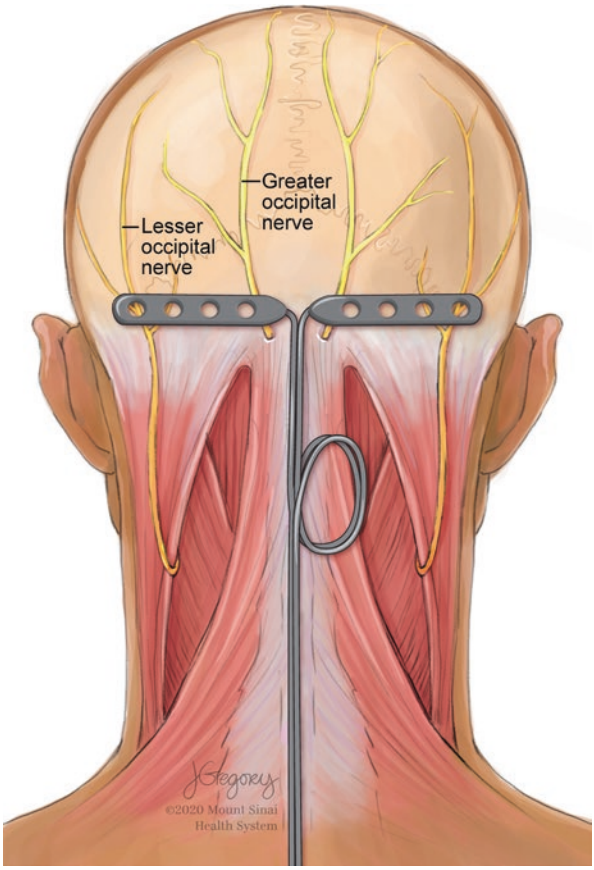

Fig. 12.1 Occipital nerve stimulation with paddle electrodes

Results

Generally, results of ONS in the context of refractory chronic migraine have been encouraging. Multiple randomized controlled trials have demonstrated efficacy in the treatment of migraine. A 2015 systematic review showed an average reduction of moderate/severe headache days by 2.5 per month compared to sham stimulation at 3 months. However, this same review also demonstrated an average reduction of 2–4 days per month from sham stimulation alone. Responder analysis at 3 months using a threshold of 50% reduction in headache days and/or pain intensity favored ONS but did not reach statistical significance [17]. Further, this review highlighted the heterogeneity of study design and outcome measures that make pooled statistical analysis difficult. Therefore, while the results in the ONS literature are generally positive, with some non-blinded and single-center studies demonstrating >50% pain reduction in 50–70% of patients [21], the grade of evidence is still considered moderate to low. Overall, the average response rate is approximately 56% for chronic migraine. Nevertheless, it should be noted that even a modest reduction in headache

severity and/or frequency can be very desirable to patients who suffer from otherwise intractable pain.

The use of ONS for cluster headache has had impressive results, with about 50% pain improvement in one-third to two-thirds of patients. A 2016 long-term follow-up study over 6 years demonstrated a 66% response rate (>50% reduction in the number of daily attacks) [18].

Hemicrania continua, a condition defined by its total response to indomethacin, has also been demonstrated to have a robust response to ONS, with 67% of long-term follow-up-patients reporting at least a 50% improvement in symptoms [12]. More extensive studies are needed to validate further the results of these relatively small series on cluster headache and hemicrania continua. Still, current evidence does suggest these patients may benefit from ONS if they are otherwise medically refractory.

Supraorbital/Infraorbital Nerve Stimulation

Pathophysiology

The precise mechanism by which migraine relief is obtained via supra- and infraorbital (SO/IO) nerve stimulation is unknown. In healthy volunteers undergoing non-invasive SO/IO nerve stimulation, an acute sedative effect has been noted. It is questionable, however, if this effect relates directly to migraine control [27]. Given the current understanding of migraine pathology, stimulation is likely to downregulate the trigeminal pain pathways.

Indication

Patients undergoing consideration for this procedure should be appropriately selected and have pain localized to the distribution of the nerves to be stimulated. A good example would be a patient with chronic frontal headache that is responsive to injection in the supraorbital ridge with a local anesthetic.

Technique

As described by Munyon and Miller, the procedure begins after a trial stimulation, most often performed percutaneously under mild sedation and local anesthesia. Following successful trial stimulation, permanent implantation is undertaken. The head may be placed in either a prone position for bilateral stimulator placement or

turned contralateral for unilateral placement. The entry point is located superior and lateral to the eyebrow to target the supraorbital nerve and just above the malar eminence for infraorbital lead placement [22]. A stab incision is sufficient to allow for the introduction of a Tuohy needle with the convex curve of the needle following the contour of the skin. Care must be taken to avoid puncturing the skin, and this may be done with constant palpation of the needle tip while advancing. The needle/stylet must be advanced past the target nerve foramen, and then the electrode introduced through the needle. The needle is then withdrawn, and the placed electrode can be connected to a stimulator to ensure the patient experiences mild paresthesia and does not experience shock-like sensation, or muscle pulling, which could indicate too superficial or too deep placement, respectively. C-arm fluoroscopy may be used to help determine the optimal final position. The lead is then tunneled subcutaneously to a distal site above the ear. Upon implantation of the permanent system, a 2 cm retroauricular incision is utilized to develop a subcutaneous pocket to anchor the lead, which is then tunneled to the usual infraclavicular site for the IPG.

Results

Large series evaluating peripheral nerve stimulation of the supraorbital and infraorbital nerves for headache are lacking. The majority of published series (Clark- 2016, Reed -2010, 2015, Sharan-2013) [23–26] focus on concurrent occipital and supraorbital stimulation for chronic migraine. Results from these series are positive, with >50% of patients receiving >50% reduction of migraine pain. However, results may not be applicable to the use of supra- and infraorbital stimulation alone.

Supraorbital Nerve Decompression

Pathophysiology

It has been postulated that migraine headaches result from the activation of the terminal branches of the trigeminal nerve. The rationale to decompress these branches is, therefore, sensible in appropriately selected patients.

Technique

Surgery for migraine was first thought to be possible in the late 1990s after Guyuron noted that migraine patients undergoing forehead rejuvenation surgery had a reduction in their migraine symptoms. A series of trials then followed to investigate this

finding, which yielded positive results. Surgery consists of corrugator supercilii muscle resection to decompress the supratrochlear and supraorbital nerves with avulsion of the zygomaticotemporal branch of the trigeminal nerve bilaterally [19]. As described by Guyuron [20], for the transpalpebral approach, a skin incision of 1 inch in length is made in the upper tarsal crease of each eyelid and deepened through the orbicularis muscle only. In the anatomic plane between the orbicularis muscle and the orbital septum, dissection is continued cephalad until the corrugator supercilii muscle is exposed. While preserving the supraorbital and supratrochlear nerves, the corrugator supercilii muscles are removed bilaterally. For the combination of corrugator supercilii resection, temporal release, and transection of the zygomaticotemporal branch of the trigeminal nerve, an endoscopic approach is described. Five half-inch incisions are made, one in the center and two on either side in the temple area. The endoscope is introduced, and a subperiosteal dissection is carried to the supraorbital rim, lateral orbital rim, zygomatic arch, and malar region. The zygomaticotemporal branch of the trigeminal nerve is then transected and coagulated. The periosteum and arcus marginalis are released over the lateral orbital region and the supraorbital area. The corrugator supercilii muscle is then exposed and removed as completely as possible.

Results

Overall, supraorbital nerve decompression has very positive results in properly selected patients. In one recent study of 30 patients who underwent this procedure for migraine, at 11-month follow-up there was a mean reduction in migraine headache episodes from 15.2 episodes per month to 1.9. Patients in this study also experienced a decrease in the mean intensity of migraine headaches from 7.3 to 1.3 on a 1–10 scale questionnaire. Nearly half of the patients reported complete elimination of migraine [19]. These results are encouraging and support data from older series [58–60]. However, it must be kept in mind that studies examining decompression surgery for headache are relatively small. Thus, the technique is not usually employed as a first-line surgical therapy.

Sphenopalatine Ganglion Stimulation

Pathophysiology

Cluster headache (CH), a primary headache disorder, is the most common form of trigeminal autonomic cephalalgia. The attack of CH pain is presently thought to involve activation of the trigemino-autonomic reflex, with the posterior hypothalamus also playing a role via a trigemino-hypothalamic pathway [33]. This model is

accepted given that it helps explain much of the semiology of CH attacks, namely, unilateral trigeminal distribution of pain, ipsilateral cranial autonomic symptoms, and a circadian episodic pattern [33]. The precise mechanism of CH pain induction is not known, but modern hypothesis implicates activation of the parasympathetic superior salivatory nucleus and sphenopalatine ganglion (SPG) parasympathetic fibers as well as the release of calcitonin gene-related peptide and vasodilation of the cerebral and dural blood vessels. This cascade leads to the activation of meningeal nociceptive fibers, which project to the trigeminal ganglion. Therefore, stimulation of the SPG is a mechanistically logical method of influencing CH.

Technique

The SPG has been implicated in headache for over a century, with various methods including surgical ganglionectomy [34], lidocaine application [35], percutaneous lesioning [36], and presently, electrical stimulation. The success of SPG-directed therapies, while robust, usually required repeated intervention due to the transient nature of the effects. Given the need for repeated invasive treatment, Ibarra, in 2007, demonstrated the use of an implantable device [37]. In 2010, Ansarinia showed acute SPG electrical stimulation terminating CH attacks within several minutes in six patients with a transient electrode implanted via an infrazygomatic approach [38].

As described by Ansarinia [38] and Narouze [36], the approach begins with the patient positioned supine on the procedure table. The pterygopalatine fossa is identified with both anterior-posterior and lateral fluoroscopy. On lateral views, an attempt should be made to superimpose both mandibular rami on each other to better visualize the pterygopalatine fossa as an "inverted vase." Following appropriate prepping and local skin and subcutaneous anesthesia, a 20-gauge needle (Medtronic Foramen Needle) is inserted at the entry point inferior to the zygomatic arch and anterior to the mandible with a projected course through the coronoid notch onto the pterygoid plate on lateral view. The needle is then marched anteriorly along the pterygoid plate and into the pterygopalatine fossa under fluoroscopic guidance. Once the needle is in place, physiologic verification of location can be performed by removing the needle stylet and introducing a single contact stimulation electrode toward the SPG. The electrode is driven at 50 Hz with 300 μsecond pulse width over varying intensities typically under 2 V until paresthesia is induced in the posterior nasopharynx and root of the nose. A chronically implanted electrode ("Pulsante" device manufactured by Autonomic Technologies, but is no longer available in the United States) is secured along the zygomatic process with a screw plate and is powered and activated via an external handheld wand to achieve on-demand SPG stimulation for cluster headache [33].

Results

The rate of success for these various SPG-directed procedures, including ganglionectomy, lidocaine application, percutaneous lesioning, and electrical stimulation, varies between 46% and 85% [33]. A 2017 systematic review investigated electrical stimulation of the SPG in 28 CH patients. Results showed significant pain relief within 15 min after stimulation in 67% of cluster attacks, with 34% of attacks completely aborted. Attack frequency also decreased from a mean of 17.4–12.5 episodes per week. Overall, 68% of patients responded to the therapy; 25% experienced pain relief in ≥50% of episodes; 36% experienced a ≥50% decrease in attack frequency; and 7% of patients experienced both [41]. Therefore, SPG stimulation represents a robust option to improve headache management in medically refractory patients with CH.

Deep Brain Stimulation

Deep brain stimulation (DBS) is not traditionally utilized for headache disorders. However, functional neuroimaging has demonstrated that the posterior hypothalamic region and ventral tegmental area are activated during CH attacks [28]. DBS for headache first began with Leone in 2001 [31], with the implantation of an electrode to the posterior hypothalamic gray matter. Further evolution through the work of Matharu has now defined the target for DBS as the ventral tegmental area (VTA) [28]. By using stereotactic image guidance, a DBS electrode can be placed into the VTA ipsilateral to the site of pain, with the device then being kept on and active at all times [29]. There are approximately 70 cases to date of open-label use of DBS to the VTA for cluster headache, with an overall response rate of 66% [30]. However, a single randomized placebo-controlled trial of 11 patients using DBS vs. sham stimulation over 1 month demonstrated no difference between the groups. It must be noted though that response to VTA DBS can take up to 3–6 months; thus, the duration of this trial may have been insufficient to prove a positive benefit. A series of six patients by Bartsch of ipsilateral posterior thalamic stimulation for CH demonstrated four out of six patients to have a profound reduction in their headache attack frequency and pain intensity over 6 months; at 17 months, three out of the four responders remained completely attack free, for an overall efficacy rate of 50% [53]. Another long-term study (5-year follow-up) of four patients implanted with posterior hypothalamic DBS for CH revealed that all four patients continued to experience significant (between 50% and 90%) reduction in headache frequency [39]. As with all surgical therapy for headache, patients must first be refractory to all other treatments. Implantation of DBS electrodes for this purpose must be performed in highly specialized centers following a multidisciplinary team review, including neurologist and psychologist input [29]. There is currently no evidence supporting the use of DBS in chronic migraine.

Transcranial Magnetic Stimulation

Pathophysiology

Transcranial magnetic stimulation (TMS) involves the non-invasive application of a magnetic coil to the surface of the scalp that induces electrical current on the cortical surface and thus alters cortical excitability. The coil current, and resultant magnetic field (up to 2 Tesla), is usually delivered in a rapidly alternating fashion (1 ms), with about 5mm^3 of cortex stimulated. Spreading waves of cortical hyper-excitability is one mechanism thought to occur at the onset of migraine headache, with resultant waves of cortical depression that follow. These changes in cortical activity are thought to be related to various aura phenomenon at migraine onset via activation of the trigeminal vascular system and the trigeminal-cervical complex [15]. TMS likely works via halting spreading cortical waves of hypo- and hyperexcitability at headache onset. TMS is postulated to activate interneurons in the second and third layers of the cortex, which ultimately synapse to pyramidal neurons of the fifth layer [16].

Technique

TMS can be delivered using multiple protocols, including single-pulse (sTMS), paired-pulse, and repetitive stimulation (rTMS). Repetitive stimulation modes allow for stimulation at low frequency (1 Hz), high frequency (5–20 Hz), or extremely high frequency (50 Hz), which is defined as a theta burst [27]. sTMS is often applied over the visual cortex to establish phosphene threshold as a means of establishing cortical excitability thresholds. Similarly, if TMS is applied to the motor cortex, motor-evoked potentials can be recorded with EMG. A train of rTMS pulses can then be delivered to the cortex at a sub-motor-threshold intensity to treat migraine. In an acute migraine, sTMS is a potential means of headache severity reduction. rTMS is believed to produce long-term changes in neuronal excitability and to provide an overall reduction in headache frequency. Results of TMS for migraine, as summarized in a 2019 systematic review, established a “moderate GRADE working group” level of evidence with respect to rTMS reducing headache frequency by >50%, as well as a reduction in headache intensity and abortive medication use [27].

Trigeminal Neuralgia

Surgical therapies for trigeminal neuralgia (TN) include microvascular decompression (MVD), glycerol rhizotomy, radiofrequency rhizotomy (RF), and gamma knife radiosurgery. Medical treatments should be exhausted before attempting any surgical therapy. The exact pathophysiology of TN is not fully understood. However,

most theories implicate either idiopathic or vascular compression–related demyelination of the proximal trigeminal sensory fibers with a resultant ectopic generation of spontaneous nerve impulses and their ephaptic conduction to adjacent fibers [55].

Microvascular Decompression

MVD via a retromastoid craniectomy approach was first successfully undertaken by Dandy in the 1920s and 1930s. Jannetta popularized and refined the procedure in the 1960s and 1970s, and today the procedure remains the most durable and definitive treatment for the majority of TN subtypes.

MVD Technique

Janetta's description of the procedure is the basis upon which modern MVD is performed [42]. The patient is first induced under general endotracheal anesthesia and positioned supine with a shoulder roll ipsilateral to the operative side. The head is turned contralaterally and placed in Mayfield three-point fixation. A lateral or semilateral position can also be utilized and depends on how mobile the patient's neck is to head rotation. The neck is minimally stretched with mild flexion and rotation approximately 10° toward the affected side, and the vertex is tilted downward approximately 10°. The occipital boss should thus become the highest point in the operative field. The ipsilateral shoulder is then taped downward toward the feet and out of the way. The patient's positioning should be further reinforced with taping to allow for the operating table to be rotated laterally. The incision is then planned as follows. First, a line is drawn from the external auditory canal to the inion starting approximately 2 cm behind the ear to approximate the transverse sinus. Next, the mastoid eminence is traced out, and this point is connected to the first line, thus approximating the sigmoid sinus and defining the transverse-sigmoid junction. A straight-line retroauricular incision is then made from approximately the top of the pinna to the mastoid notch, and dissection is carried through the musculature to the skull. The identification of the digastric groove line also serves as a marker for the junction of the sinuses. A 3 cm craniotomy is then created just caudal to the transverse-sigmoid junction, taking care to stay inferior and posterior to the asterion. Any mastoid air cells should be carefully waxed. The dura is then opened in a curvilinear fashion paralleling the transverse-sigmoid junction, and the dura anterior to the incision is tacked up using suture. The next goal of surgery is careful drainage of CSF. A flexible rounded brain retractor is inserted with a cottonoid over the cerebellar surface, directed toward the tentorium and petrous ridge junction. Care must be taken not to tear any branches of the petrosal vein. After appropriate CSF drainage, the retractor is advanced. The vestibulocochlear and facial nerves are encountered first and most superficially, with the trigeminal nerve deeper and more superiorly at the apex of the exposure. At this stage, the point of neurovascular

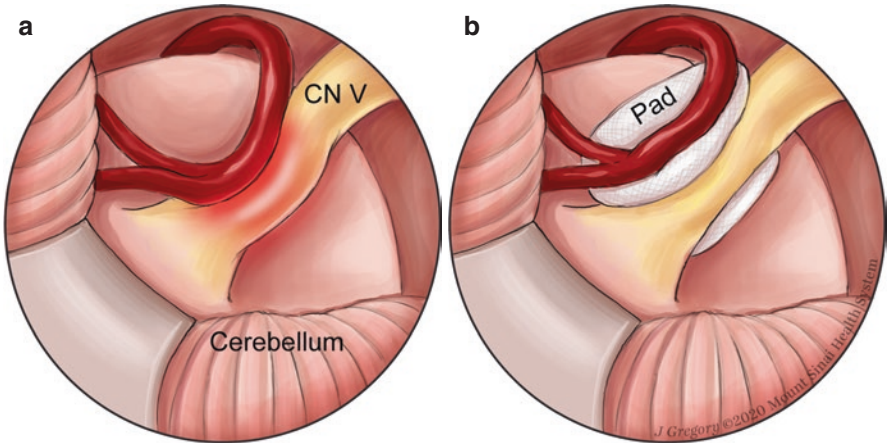

Fig. 12.2 (**a**) Typical neruovascular conflict of superior cerebellar artery and CNV (**b**) Teflon patty insertion to separate the artery from the nerve

conflict (usually a loop of the superior cerebellar artery) is identified, and the artery is separated from the nerve with a piece of Teflon. The procedure concludes after achieving hemostasis, watertight dural closure, replacement of the craniotomy flap with bone cement supplementation, re-waxing any mastoid air cells, and performing a multilayer muscle and skin closure (Fig. 12.2).

Results

MVD remains an extremely durable surgical intervention for the treatment of TN. At 10 years, approximately 70% of patients remain pain-free and off medication [43], with initial postoperative success rates of >90% within 1 year in a recent meta-analysis [45]. Furthermore, in the setting of CH, MVD has been demonstrated in a series by Jannetta [32] to achieve favorable results (>50% headache pain reduction) in 73% of chronic CH patients and even up to 90% pain reduction in 50% of these patients at early follow-up. Long-term follow-up saw the success rate fall to 47%. There is a low risk of sensory disturbance from this procedure, like anesthesia dolorosa, compared to destructive procedures.

Stereotactic Radiosurgery: Gamma Knife

Radiosurgery for TN was first championed by Lars Leksell in 1951, using a dental X-ray machine affixed to a guiding device. The field has advanced since that time. Current techniques use gamma knife (GK) radiosurgery to target the trigeminal nerve just anterior to the pons using high-resolution MRI.

Indication

By the end of the twentieth century, microvascular decompression via craniotomy had emerged as the "gold standard" for the treatment of medically refractory TN in eligible patients. However, there exists a subset of patients who remain poor surgical candidates [44]. Cardiac or pulmonary complications, altered hematologic coagulation parameters, advanced age, and infirmity to undergo craniotomy, or simply patient preference and comfort levels, may all render a patient ineligible for craniotomy.

Technique

High-resolution volumetric MRI is obtained for radiosurgical planning, usually consisting of FIESTA or CISS sequences to highlight the trigeminal nerve at the pons. The procedure begins with rigid fixation of the patient's head in an MRI compatible Leskell stereotactic frame with a local anesthetic used at the pin fixation sites on the scalp along with mild intravenous sedation. High-resolution MRI images of the entire head (including 3D volumetric gradient pulse, T2-weighted 3D volumetric, and T1 and T2 sequences) are obtained. Dose planning is then performed with attention given to the trigeminal nerve anterior to the pons using small collimation (1–24 mm isocenters) [44]. The treatment plan is optimized after definition of the maximal dose to the nerve target is determined, along with dosing delivered to any adjacent structures, including the brainstem. A dose of 80–90 Gy is typically prescribed by most centers to the 100% (maximum) isodose line [44]. A maximum dose of 80 Gy is associated with a low (10%) rate of facial sensory dysfunction with a robust 80% success rate for significant pain relief. Clinical trials comparing one vs. two isocenter radiosurgery (to include a longer segment of the trigeminal nerve in the treatment plan) demonstrated no difference in pain relief but did show an increased rate of sensory dysfunction.

Results

GK radiosurgery usually begins to take effect within several months after treatment, most commonly within 1–2 months, although reports of treatment effect after 6 months are infrequently reported. GK delivers an overall initial success rate of 72% before 1 year, with pain-free efficacy rates dropping to 46% by 5 years [45, 54]. Approximately 70% of patients still enjoy partial pain relief by 3-year follow-up. Therefore, in both short-term and long-term follow-up, MVD remains superior to GK. However, GK remains an excellent option for patients unable or unwilling to undergo craniotomy.

Radiofrequency Rhizotomy

The first radiofrequency (RF) lesions to the trigeminal ganglion were made in 1932 by Kirscher using large (1 cm) electrodes [46]. The approach was not immediately popular due to damage to adjacent cranial nerves and associated neurological deficits. Later, White and Sweet refined the procedure with the use of short-acting anesthetic to produce brief analgesia and immobility, along with electrical stimulation for localization of the electrode within the target nerve, and finally a thermistor within the RF electrode to monitor temperature during the procedure [47].

Indication

RF rhizotomy, in general, represents an effective outpatient procedure with modest durability that can be offered to patients who are not candidates for craniotomy or GK.

Technique

The patient is positioned supine on the procedure table, and fluoroscopy is used to identify the foramen ovale in either a submental vertex or oblique fluoroscopic projection. After induction of anesthesia and maintenance of the airway with an appropriate nasopharyngeal airway device, the patient is prepped and draped; 1% intradermal lidocaine is injected with a 23 g needle into the cheek along the planned trajectory. A point 2.5 cm lateral and 1 cm inferior to the labial commissure is marked out. An 11 blade is used to make a stab incision at this point, and a 22 g RF cannula is inserted and directed to the foramen ovale. One finger is placed against the buccal mucosa to strictly prevent the violation of the oral cavity as the cannula is advanced. The trajectory proceeds along a path that is at the intersection of two planes: (1) from the point of insertion to a point 3 cm anterior to the ipsilateral tragus and (2) from the point of insertion to a point at the medial border of the ipsilateral pupil. This defines the classic Hartel technique. At this point, the cannula is advanced until the skull base is reached, radiographically anterior to and in line with the foramen ovale [48]. On AP fluoroscopy, the needle is seen being directed toward the inferomedial aspect of the orbit, while on lateral fluoroscopy, the needle is aimed at the angle of the clivus and petrous ridge junction. Upon entry into the foramen, the fluoroscope is placed in the lateral position, and the cannula is advanced. For V1 or V2 trigeminal neuralgia, a curved electrode is often needed, whereas a straight electrode is usually sufficient for V3. The trigeminal cistern lies just anterior to the junction of the clivus and petrous bone on lateral fluoroscopy. Positioning the electrode point more toward the posterior clinoid will allow for the acquisition of the

more medial V1 and V2 divisions [47]. The stylet is then removed from the cannula, and gentle aspiration is performed to ensure no CSF or blood return. Injection of 0.5 mL of contrast dye can help with confirmation that the dura has not been violated [49]. At this point, test stimulation is performed at 50 Hz, 0.1–0.5 V, and 1 ms pulse duration to verify that paresthesia is experienced by the patient in the appropriate trigeminal distribution. After successful trial stimulation, RF lesioning can then be performed at 60 °C for 60 s [49].

Another approach, tailored to patients with refractory TN (or severe post-herpetic, malignancy-related, or glossopharyngeal neuralgia), is CT-guided trigeminal tractotomy/nucleotomy, described by Kanpolat [57]. This technique involves the injection of iohexol into the subarachnoid space by lumbar puncture followed by CT-guided advancement of the lesioning electrode via the atlanto-occipital interspace toward the spinal cord. It should be again emphasized that this technique is reserved only for the most refractory cases of TN and facial pain, given its destructive nature as well as effects on sensory innervation of the seventh, ninth, and tenth cranial nerves. While traditional RF rhizotomy is only partially destructive and thus leaves other surgical options open for the future, the CT-guided trigeminal tractotomy-nucleotomy is definitively destructive and leaves little option for further treatment (Fig. 12.3).

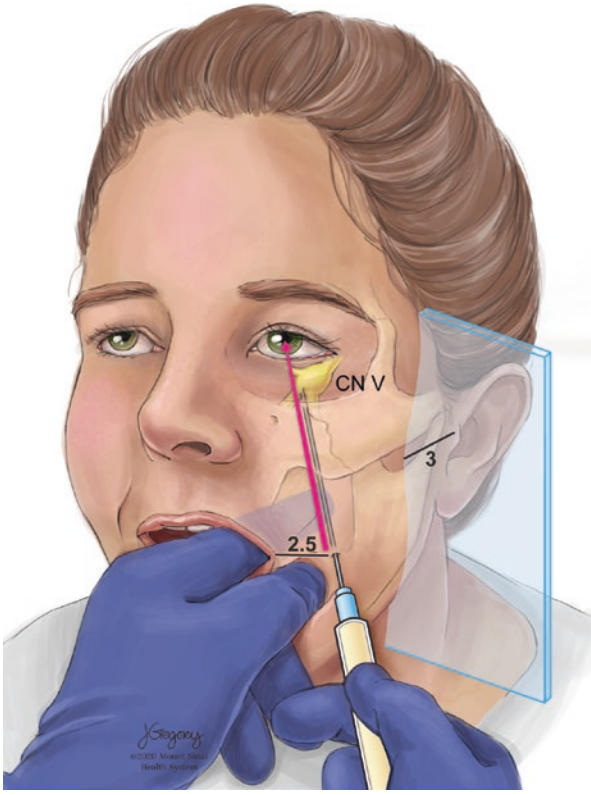

Fig. 12.3 Hartel Technique

Results

Initial pain relief following RF rhizotomy approaches MVD efficacy with a greater than 90% patient response. However, long-term results are less robust, with up to 20% of patients having a recurrence of their pain at 1 year [49]. A 2019 meta-analysis demonstrated RF rhizotomy to have a lower rate of postoperative herpes eruption (2.4% vs. 8%) compared to glycerol rhizotomy [52].

Glycerol Rhizotomy

Indication

The indications for glycerol rhizotomy mirror those of RF lesions, as previously discussed. The procedure was first reported in 1978 when Leksell and Hakanson injected tantalum dust mixed with glycerol into the trigeminal cistern to visualize the trigeminal nerve in preparation for gamma knife radiosurgery. Immediately following injection and prior to GK therapy, they observed that many patients reported significant pain relief [50].

Technique

Targeting of the foramen ovale is done in the same way as for RF lesioning, as discussed previously. A 20 g spinal needle is used, however, for penetration of the foramen ovale. Once the trigeminal cistern has been entered, the operator should verify CSF egress from the needle. The patient is positioned with the head of the bed at 60° to perform a contrast cisternogram to assess the volume of the trigeminal cistern as a guide for later glycerol volume injection. A tuberculin syringe is used to inject sterile iohexal in 0.05 mL increments under fluoroscopic guidance until the contrast is seen as overflow out of the cistern, usually about a 0.25 mL average volume [51]. The cistern typically appears to be the shape of a bowling-ball on its side. The contrast then escapes the cistern via spontaneous drainage (sometimes requiring the patient to be placed back into the supine position). At this point, with the patient at 60°, the glycerol injection is performed (99.9% anhydrous glycerol with radiopaque tantalum powder) to a volume determined by the prior contrast injection. The technique for filling the cistern may vary, with operators electing to fill the entire cistern for patients with multi-division pain or allowing the glycerol to float on top of the contrast material in patients with isolated V1 pain [51]. Given the lighter density of glycerol, it tends to float on top of the contrast material and exert its effects on upper-division fibers first. After injection, the needle is removed, and the patient is kept in the upright position for at least 2 h to prevent the escape of glycerol into the posterior fossa.

Results

Outcomes following glycerol rhizotomy are similar to RF lesioning, with pain relief occurring in about 80% of patients either immediately following the procedure or within 3 weeks. At 5 years, pain relief is between 20% and 30% and a median duration of pain relief of about 21 months [40].

Conclusion

Surgical intervention remains a relatively sparsely utilized technique in most forms of headache disorder management. Patients who come to surgical intervention must have failed all other treatments given the invasive nature of the procedures. The evidence for various headache conditions remains modest (excluding trigeminal neuralgia where MVD has shown superior results). However, there are encouraging results for chronic migraine, cluster headache, hemicrania continua, and headaches of occipital and cervicogenic origin. Further research into both the underlying pathophysiology of various headache disorders and the mechanism of action of various surgical interventions needs to be undertaken if there is to be continued progress in defining the most appropriate and efficacious surgical interventions for headache.

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