Chapter 3
Trigger Identification and Elimination

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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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