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Triggers, Protectors, and Predictors in Episodic Migraine.

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Purpose of review:

A wide variety of triggers prompt attacks in episodic migraine. Although experimental triggers such as glyceryl trinitrate reliably produce migraine, natural triggers are much less predictable and vary in importance between individuals. This review describes the most common triggers in episodic migraine and strategies for managing them in clinical practice.

Recent findings:

Multiple migraine triggers have been established based on patient surveys, diary studies and clinical trials. Stress, menstrual cycle changes, weather changes, sleep disturbances, alcohol and other foods are among the most common factors based on patient surveys. Clinical studies have verified that fasting, premenstrual periods in women, "letdown" after stress and likely low barometric pressures are migraine triggers. Premonitory symptoms such as neck pain, fatigue and sensitivity to lights, sounds or odors may mimic triggers.

Summary:

Multiple studies clearly demonstrate triggers in episodic migraine, often related to change in homeostasis or environment. Many common migraine triggers are not easily modifiable, and avoiding triggers may not be realistic. Healthy lifestyle choices such as exercise, adequate sleep, stress management and eating regularly may prevent triggers and transformation to chronic migraine over time.

Keywords:

Episodic migraine, fasting headache, migraine triggers, food triggers, menstrual migraine, weather in headache, migraine diaries.

Introduction:

Migraine and related disorders such as probable migraine are among the most common medical disorders and the most frequent reason for seeing a neurologist, although many with the disorder do not seek treatment (1). In one study, migraine or probable migraine had a combined 1-year

prevalence of 22.6% in women and 9.6% of men (2). Migraine is also more prevalent in those with lower socioeconomic status, and migraine is a significant cause of work absence and disability (3). While most patients with episodic migraine remain that way, 2.5% of persons with episodic migraine per year develop chronic migraine (4).

Patients with migraine are keen to learn about factors activating migraine and report a number of triggers. Exogenous compounds such as glyceryl trinitrate (5) and prostaglandin E2 (6) reliably trigger migraine in susceptible subjects. However, lower-intensity "natural" triggers such as stress or bright lights do not reliably cause migraine attacks (7). Attempts to avoid triggers are often unsuccessful and cause avoidance of enjoyable social or leisure activities (8). Many patients with episodic migraine experience a wide variability of attack frequency month-to-month. In most, these fluctuations are not easily explained by common triggers. Prodromal symptoms in migraine such as mood changes or food cravings are also common and may be confused for triggers (9). This unpredictability measurably impairs quality of life, and may cause significant disability and anxiety even between attacks (10).

Episodic migraine is a paroxysmal disorder and attacks typically occur randomly, often in clusters lasting days or weeks. Non-linear mathematics, and chaos theory in particular, may better explain the seemingly arbitrary nature of migraine attacks (11) and its underlying physiology such as cortical spreading depression (12). This may explain why most patients cannot find triggers which invariably produce migraine. Non-linear mathematical concepts, such as fractal scaling, helps explain large differences in scale in disorders such as epilepsy due to small changes in a given variable (13). While there is no universally established physiological measure of migraine such as the electroencephalogram in epilepsy, autonomic nervous system functioning changes such as heart rate or ECG changes (14) or changes in mood or stress levels may predict migraine attacks (15). Future models may anticipate increased migraine severity or chronification, allowing earlier, more effective intervention.

This review focuses on the evidence for specific triggers for migraine including toxicity or withdrawal, changes in homeostasis and other stressors. Proven secondary causes of headache such as vascular disorders, intracranial mass or infection, chronic infection, autoimmune disorders such as hypothyroidism, sleep apnea, and headache due to high or low pressure headache syndromes will not be considered in this review. Head trauma or overuse of medication may also precipitate or worsen migraine, but will not be considered a trigger for the purposes of this review.

Which triggers are most prevalent in episodic migraine?

Numerous clinical studies have focused on migraine triggers, either by patient self-report, clinician-administered questionnaires or using patient diaries. Large systematic reviews have confirmed the most common triggers in migraine with stress, auditory stimuli, fatigue, fasting and menses the most commonly implicated respectively (18). A common link between triggers is

alterations in daily activity or environment which increase migraine susceptibility (16). Kelman et al reviewed triggers in 1,750 patients with migraine and found 76% of respondents, with an average of 7 each. Patients were more likely to select triggers from a provided list than spontaneously report them. The most common triggers included stress, menses, fasting, weather changes, sleep disturbances, odors, alcohol, heat and foods (17). Combining multiple factors is probably more potent, and in patients with infrequent migraine may be necessary to trigger an attack. For example, in one study there were clear differences in coping, stress and migraine based on timing of the menstrual cycle (18). It is not clear if triggers are more or less important in those with and without aura, or if triggers are specific to migraine compared to tension-type headache. As an example, one study suggested food triggers are more common in migraine than tension-type headache (19).

Due to the fact that natural migraine triggers are individualized and may be unlikely to trigger attacks unless other conditions are present, there have been recent attempts to use sophisticated statistical analysis to discover migraine triggers and protectors. The Curelator Headache web-based platform, for example, attempts to determine associations between one or many combinations of factors and triggers to predict migraine attacks in individuals based on their data (20). In a study of 326 patients with migraine, this program generated an average of 4 factors associated with attacks per patient and 85% of factor profiles were unique to the individual (21). Some of the most common factors predicting migraine such as neck pain and tiredness were likely premonitory symptoms. Exposure to odors (25.2%) and lights (24.8%), missed meals (20.6%), and private stress (10.1%) or work stress (8.6%) were among the most common implicated factors (21).

How accurate are patients in reporting triggers?

It can be challenging to distinguish between migraine triggers and premonitory symptoms which occur 2-48 hours prior to migraine. The prevalence of premonitory symptoms in migraine varies from 30-80% (22, 23). Common premonitory symptoms which may be confused for triggers include neck pain, light sensitivity (24), and food cravings. As an example, the association with chocolate and migraine is likely a result of food craving prior to attacks. Placebo-controlled studies have failed to show chocolate triggers migraine (25).

In general, patients self-report more triggers when compared to diary studies. Prospective diaries are more reliable means to establish connections with migraine and specific triggers(9). Some patients may overestimate the effect of specific triggers such as weather(26), or fail to recognize subtle triggers which may increase susceptibility. While many have an inaccurate perception of their actual triggers, on the day of an attack patients are fairly good at predicting migraine. Griffin et al found that among subjects are “almost certain” a migraine would occur, 93% actually developed headache (27). Nocebo is a major problem in headache, both in clinical trials and practice (21). The suggestion that a specific trigger will cause migraine attacks may

contribute to expectancy mechanisms have been established as a cause of increased symptoms in other pain disorders (22).

Dietary triggers in migraine

Dietary studies which attempt to link specific foods to migraine are limited by the lack of placebo, the difficulty in distinguishing between premonitory food cravings and triggers, and the fact that the foods are more likely to be contributory than the sole cause of a migraine attack (21). Several studies have explored the relationship of migraine to food allergies and proposed treating migraine with specific diets such as elimination (28, 29). Fasting and caffeine withdrawal are two of the most common migraine triggers, but several studies have evaluated the role of diets and specific foods or additives as a triggers of migraine.

Fasting is among the best studied and most reliable natural migraine triggers, and becomes more common with longer fasts (30). Dehydration is unlikely the cause of fasting headache (31), but changes in sympathetic activity due to hypoglycemia may play a role (32). Multiple clinical studies support the relationship of fasting and migraine, including studies of fasting for religious reasons such as Ramadan (33) or Yom Kippur (34). Taking long-acting acute medication such as a non-steroidal or frovatriptan (35) may prevent migraine associated with fasting. Nighttime snacking and to a lesser extent, a late dinner, was protective against migraine related to stress in one study (36). A few studies also suggest water-deprivation as a trigger for migraine (37).

Alcohol is one of the most commonly cited migraine triggers, but population and clinic-based studies suggest people with migraine are less likely to drink, and that alcohol is not linked to migraine based on diary studies (38). A minority of persons with migraine may develop immediate headache from alcohol or some other component in red wine (39), but delayed headache is much more common. It is likely that alcohol metabolites such as acetate cause headache rather than alcohol itself, explaining the delayed effect of alcohol for producing “hangover” headache (40). Alcohol metabolism may influence migraine risk and one study found specific genotypes of alcohol dehydrogenase 2 enzymes either decrease migraine risk overall, or increase risk of migraine from alcohol (41).

Multiple studies have attempted to explore the role of specific foods and additives in triggering migraine. Caffeine is effective in acute migraine in combination with analgesics, but may cause dependence and caffeine withdrawal headache with frequent use. Caffeine discontinuation improved responsiveness to migraine treatment in one study (42). Dairy is a commonly reported migraine precipitant although patients are more likely to identify cheese or yogurt as a trigger than milk (43). Headache is the most common neurological symptom in patients using aspartame, an artificial sweetener. The link between aspartame and migraine is relatively weak with some studies being negative (44), but specific patients may be particularly susceptible (45). Nitrites such as in preserved meats may trigger migraine in some individuals (46). While nitric oxide is important in migraine pathophysiology (47), nitrites are not a common trigger in diary

studies and drugs targeting nitric oxide synthase are not very effective with significant safety issues (48). Biogenic monoamines such as tyramine have been postulated to be an important trigger for migraine based on the possible association of dairy, alcohol, chocolate and migraine (49), however, more recent studies with an oral challenge refute this link (50). The link between histamine in food and migraine also appears unlikely based on the failure of histamine antagonists to prevent migraine attacks related to food (51). Glutamate, an excitatory and pro-inflammatory neurotransmitter, enhances food flavor. Migraine patients commonly cite foods containing umami and monosodium glutamate (MSG) as migraine triggers (52), although the effect of MSG in triggering migraine is likely overstated (53).

A few studies have attempted to evaluate the role of diet in general in migraine. One large questionnaire study of 3,069 women in the National Health and Nutrition Examination Study found that women with migraine had a significantly lower diet quality as measured by the Healthy Eating Index (54). In one study, a low-lipid diet appeared to reduce severity and frequency in a population of adults with episodic or chronic migraine (55). A randomized crossover study of 42 adults with migraine found a low-fat vegan diet was more effective than a placebo supplement in improving headache severity during the study period (56). Ketogenic diets may improve migraine based on a few small case series in adults and children, but compliance can be difficult (57). In patients with irritable bowel syndrome and migraine, food elimination based on IgG antibodies may improve migraine frequency as well as bowel symptoms (58). Obesity is a risk factor for chronic migraine (59) and dietary-induced obesity may increase migraine by altering release of calcitonin gene-related peptide and increasing trigeminal sensitization (60). It is unclear if diet alone or lack of physical activity (61) that leads to increased migraine frequency in obese patients.

Menstrual changes as a migraine trigger

Menses is perhaps the most common migraine trigger in women. In one population-based study, over half of women with migraine reported an increased rate of migraine related to menses, although only a small minority (3.9%) had migraine during menstruation (62). Diary studies confirm that menstruation can trigger migraine, perhaps more so in those with aura (63). Migraine attacks during menses may be more severe, with reduced response to acute medication such as triptans (64). Estrogen withdrawal prior to menses is likely the cause of menstrual migraine and explains why migraine onset often commences prior to menstruation onset or on the first day (65). For a significant minority of women, menstrual-related migraine may be more likely to occur towards the end of their cycle suggesting a relationship to blood loss or anemia (66).

Weather triggers in migraine

Multiple studies have considered the relationship between migraine or headache and environmental factors such as weather. High altitude is a proven trigger of headache especially

during rapid ascents (67). Living at high altitudes may cause chronic headache, especially in those lacking genetic adaptations to adapt to hypoxia (68).

Several clinical studies have attempted to find correlations between documented migraine attacks and weather, focusing on variables such as barometric changes, lightning, temperature, and precipitation. Prince et al reviewed calendar data of 77 subjects with migraine and found 39/77 (50.6%) were sensitive to at least 1 weather factor, although a few patients who felt they were sensitive to weather changes were not (26). Hoffman et al reviewed the 12-month calendar data of 20 subjects with migraine and found 6/20 were significantly sensitive to weather changes, with lower temperature and higher humidity being associated with increased headache intensity (69). A 1-year calendar study in Japan found 18 of 28 patients had migraines related to weather changes, most commonly related to low barometric pressure (70). A non-clinic web or smartphone study of volunteers in Germany found an increase rate of migraine reports on days of significant weather changes, in particular a 5°C rise in temperature (71). Cooke et al studied the effects of warm westerly chinook winds in Alberta in migraine. The 75 subjects with at least 2 months were more likely to experience migraine on pre-chinook days and days with chinook winds than non-chinook days, although only 2 subjects were sensitive to both conditions (72). Zebenholzer and colleagues reviewed 90-day calendar data in winter from 238 subjects with migraine and attempted to find correlations between meteorological parameters and weather situations. There was some increase of migraine on days with high pressure, low wind speed and increased sunshine duration, but none of these associations proved statistically significant. They also found no correlation between subjective weather perceptions and migraine, and concluded the influence of weather in migraine is small and questionable (73). A review by Bolay and Rapoport (74) suggest low barometric pressures alone are probably unlikely to trigger migraine unless accompanied by other factors such as hypoxia at high altitudes or Saharan dust (75). Finally, a study of 90 patients in Ohio and Missouri suggested lightning was an independent risk factor for migraine, even when adjusting for other variables (76).

A few studies have attempted to find correlations between weather data and emergency department (ED) visits for headache or migraine. Mukamal et al performed an ED case-crossover study of 7,054 patients seen for headache and reviewed meteorological data for the few days prior to their visit. ED visits for headache or migraine were more frequent during days of higher mean temperatures in the 24 hours before the visit, and there was a weaker correlation between low barometric pressures 48 to 72 hours before hospitalization (77). Yilmaz et al in a review of 3,491 patients admitted to the ED for migraine found significant associations with high temperatures and low humidity (78). Elcik et al reported increased ED visits for migraine on days with tropical air masses over a 7 year period in the Raleigh-Durham metro area (79). Villeneuve et al, on the other hand, found no significant relationship between 4,039 ED visits for migraine and any weather condition(80).

Air pollution may be a trigger for headache as well. A Canadian study found that increased ambient air pollution, especially nitrogen dioxide, was associated with increased emergency

department visits for headache during the day of exposure and the following day (81). However a separate US study did not find a statistically significant association between common pollutants and emergency visits for headache. (77).

In patients living at extreme latitudes such as the Arctic Circle, seasons and sunlight may precipitate migraine. In a questionnaire study of residents in Northern Norway, subjects with migraine reported more attacks in the summer, while non-migraine headaches were more common in the darker season (82). Subsequent diary studies have failed to prove this seasonal migraine link (83) but have suggested sunny weather may trigger migraine (84).

Sensory stimuli as a migraine trigger

Visual, noise, olfactory and other sensory stimuli exacerbate migraine intensity and may cause migraine in vulnerable individuals. Individuals with migraine have lower thresholds of discomfort to stimuli such as lights, sounds, odors, as well thermal and mechanical stimulations. A lack of habituation (85) and alteration in the processing of sensory stimuli likely explain these differences (86). Unfortunately it can be difficult to sort out if sensory stimuli are triggers or if patients with migraine simply become more sensitive to stimuli in the premonitory phase prior to an attack (87).

Multiple types of visual stimuli have been cited as a trigger for migraine. Tekatas and Mungen described 16 patients with sunlight as a trigger – within a mean exposure time of 5-10 minutes in the summer and 60 minutes in the winter (88). Optokinetic stimulation in a laboratory setting may trigger migraine, photophobia and nausea (89). Specific striped patterns are especially likely to trigger migraine, which may be alleviated by color filters (90, 91). Light exacerbates migraine in patients without visual perception as perceived in the thalamus (92). Green light, relative to other frequencies, is less likely to be bothersome (93).

Osmophobia is common during migraine, and may be a relatively specific symptom for the disorder (94). Odors are among the most common reported triggers of migraine in surveys with 70% of patients in one study reporting odors trigger attacks (95). Patients with migraine report multiple types of odors as triggers for migraine such as perfumes, paints, gasoline, bleach and rancid smells (96). Environmental odors such as smoke and exhaust fumes also commonly affect migraine in children and adults (97).

Stress as a migraine trigger

Stress is perhaps the most common self-reported trigger of migraine, and many studies have been able to demonstrate a link between chronic stress, pain, migraine and catastrophic thinking (98, 99). Retrospective and prospective diary studies, however, are not typically able to confirm the association between stressful days and acute migraine attacks. Wober et al assessed the relationship of multiple trigger factors to migraine and found while migraines were less likely to persist on holidays/days off, relaxation did not influence the occurrence of migraine (100).

Fatigue was more common prior to migraine in this study but not mental exhaustion or insomnia, which implies it may represent a premonitory symptom, rather than a cause of migraine (100). Lipton et al found that migraine is more likely to occur immediately after periods of reduced stress – suggesting that "let-down" headache is probably more common than acute stress-related migraine (101).

Poor sleep quality is commonly cited as a trigger for migraine, and in many patients help to treat an attack (102). Casein kinase Iδ mutations are associated with advanced sleep phase disorder and migraine (103). While sleep disturbances are a commonly reported trigger, diary studies do not consistently demonstrate it as a risk factor for migraine. Peris et al found that restless sleep was a risk factor for migraine in only 25.2% of individuals (21). Seidel et al found that while sleep quality is reduced in migraine, rates of fatigue and daytime sleepiness are similar to controls, suggesting poor sleep is caused by migraine, not the other way around(104).

Advising Patients on Triggers and Protectors: A Practical Approach

Focusing on triggers as a way to prevent migraine appeals to patients and clinicians wanting to promote wellness and reduce medication use. Successful treatment of migraine, like many other chronic illnesses, necessitates involving patients in their care, encouraging proactive behaviors and using a "patient-centered care" approach(105). Focusing extensively on migraine triggers during an office visit, however, may have negative consequences: (1) patients may feel "blamed" or stigmatized for having a migraine, (2) migraine triggers may be impossible to figure out - especially in those with very frequent or infrequent attacks, (3) the triggers may not be avoidable, (4) focusing on triggers can increase anxiety or lead to anticipation of attacks, and (5) it does not address the underlying cause of the disorder. A focus on avoiding triggers may in fact be harmful. Avoiding stress in chronic pain is less effective than coping or adaptive strategies and may lead to anxiety, reduced physical activity, increased disability, and catastrophic thinking (106, 107). A recent study by Martin et al found the standard advice to avoid triggers was not effective in reducing migraine compared to a waitlist control group, and less effective than cognitive therapy or a "learning to cope with triggers" approach (108). With this in mind, here are a few strategies to utilize when advising patients with migraine on triggers.

1. **Keep a headache journal or calendar.** Patients with migraine have a difficult time remembering their migraine frequency or severity month-to-month and there are multiple calendars specifically designed for migraine (109). Keeping a regular diary eliminates recall bias and focuses on overall migraine control rather than the last few days or weeks. Encouraging patients to journal symptoms or factors important to them is worthwhile, for example missed activities or days from work, nausea or vomiting, acute medication use, and less common complications such as weakness of vertigo. In some cases, journaling allows the discovery of unrecognized triggers amenable to treatment such as caffeine withdrawal on weekends or menstrual migraine. It may also help patients realize some perceived triggers are not as reliable as believed. Newer headache journalizing aps which

identify triggers and protectors using mathematical modelling may empower patients to better understand their individual triggers (21).

2. **Focus on healthy lifestyle choices rather than trigger avoidance.** Maintaining a healthy weight, good sleep, and regular exercise are protective factors in migraine against the development of chronic migraine. Exercise in some studies is as good as or superior to available preventive medications (110). Stress is unavoidable and exposure to migraine triggers such as noise may actually improve tolerance (111). While weather changes may trigger migraine, the magnitude of effect is small and unlikely to be treatable. While it is worthwhile to screen for some dietary triggers such as excessive alcohol or aspartame consumption, it is probably better to avoid recommending a specific diet for migraine as dietary factors vary significantly from person to person.

3. **Recognize "cephalgiaphobia" and treat it aggressively.** Cephalgiaphobia is the fear of having migraine between attacks (112). While this worry is understandable, the presence of cephalalgiaphobia in episodic migraine is an important predictor of chronification and medication overuse (113). Query patients if they worry about migraine when they are headache-free, or restrict activities due to fear of migraine. Finding effective acute medication may reduce anxiety, improve confidence and reduce the risk of chronification (114). The use of standardized psychological assessment techniques such as the Millon Behavioral Medicine Diagnostic, Minnesota Multiphasic Personality Inventory Form or Chronic Pain Acceptance Questionnaire may illuminate behavioral factors which may interfere with effective treatment (115) and suggest the effectiveness of a cognitive behavioral approach. Biofeedback is particularly helpful in migraine management, even in those without anxiety or somatization (116).

4. **For frequent attacks, recommend prevention.** For patients with very frequent migraine, it is impossible to sort out triggers. Attempting to avoid triggers is unlikely to help. Patients may decline preventive therapies as they might hope to improve by eliminating triggers such as stress or starting a new diet. While positive behaviors should be encouraged, it is probably worth offering additional effective preventive medication in most of these cases. The removal of a stressful situation or quitting work is unlikely to improve migraine (101) by itself. Explore reasons for avoiding prevention such as cost or fear of side effects (117). Review how preventive therapy treats the underlying cause of migraine and its role in decreasing brain excitability and vulnerability to attacks.

Conclusions:

Multiple factors are verified triggers in chronic migraine including stress, fasting, weather changes, and menses. Many of these factors are not easily modified, and premonitory symptoms may be confused for triggers. Strategies for managing migraine triggers include keeping a headache diary, focusing on healthy lifestyle choices and using prevention.

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