Migraine Triggers: What is the Evidence?

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Disclosures

- I have no disclosures
Objectives

- Gain insight into potential triggers of migraine
- Have the capacity to identify recent (1990 – Present) peer reviewed evidence for common triggers for migraine
- Be capable of applying evidence of migraine triggers to improve patient education on how to recognize and avoid them
Importance of Understanding Headache Triggers

- It can help identify mechanisms to better understand migraine
- It can help provide targeted treatments
- Patients can attempt to prevent migraine attacks by recognizing triggers and avoiding them
Proposed Mechanisms of triggers

- Levy, et. al. proposed that triggering factors converge on a single biological process that promotes activation of meningeal nociceptors leading to inflammation.\(^2\)
- Another mode proposed by Levy, et. al. is that different factors activate different pathways and all of them can elicit activation on meningeal nociceptors.
- Martin, et. al. propose that triggers can have a direct effect on excitatory or inhibitory neuroreceptors in cerebral structures that include cortex, thalamic nuclei, brainstem trigeminal nuclei, modulatory pathways in the brainstem (locus coereleus, dorsal raphe, periaqueductal gray) or the limbic system.\(^3\)
- Martin et al. also suggested that triggers can cause direct release of endogenous neuropeptides or neurotransmitters that can affect the structures mentioned above or that could lead to excitation of pathway of cortical spreading depression.\(^3\)
Documented Precipitants of Migraine

- Diet
  - Hunger
  - Alcohol
  - Additives
  - Certain foods
- Chronobiologic
  - Sleep (too much or too little)
  - Schedule changes
- Hormonal changes
  - Menstrual cycle
- Environmental factors
  - Light glare
  - Odors
  - Altitude
  - Weather Change
- Head or neck pain
  - Preceding migraine
- Physical exertion
  - Exercise
  - Sexual activity
- Stress and anxiety
  - Letdown
- Head trauma
- There are other endogenous factors as well
### Table 6. STRENGTH OF EVIDENCE* OF MIGRAINE TRIGGERS

<table>
<thead>
<tr>
<th>Trigger Factors</th>
<th>Strength of Evidence</th>
<th>Migraine Trigger</th>
<th>General Headache Trigger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>Strong</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Menstruation</td>
<td>Strong</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Caffeine withdrawal</td>
<td>Strong</td>
<td>Unknown</td>
<td>Yes</td>
</tr>
<tr>
<td>Visual stimuli</td>
<td>Strong</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weather changes†</td>
<td>Strong</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Moderate</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Fasting</td>
<td>Moderate</td>
<td>Probable</td>
<td>Yes</td>
</tr>
<tr>
<td>Sleep disturbances</td>
<td>Moderate</td>
<td>Possible</td>
<td>Yes</td>
</tr>
<tr>
<td>Wine</td>
<td>Moderate</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>MSG‡</td>
<td>Moderate</td>
<td>Unknown</td>
<td>Yes*</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Moderate</td>
<td>Yes</td>
<td>Unknown</td>
</tr>
<tr>
<td>Smoking</td>
<td>Weak</td>
<td>Not proven</td>
<td>Not proven</td>
</tr>
<tr>
<td>Odor</td>
<td>Weak</td>
<td>Not proven</td>
<td>Not proven</td>
</tr>
<tr>
<td>Chocolate</td>
<td>Weak</td>
<td>Not proven</td>
<td>Not proven</td>
</tr>
<tr>
<td>Tyramine</td>
<td>Weak</td>
<td>Not proven</td>
<td>Not proven</td>
</tr>
</tbody>
</table>

*The strength of evidence was defined as follows: (1) strong—at least two prospective randomized, controlled or diary studies confirming an association with no dissenting studies; (2) moderate—at least one randomized, controlled trial or a prospective diary study confirming an association with no dissenting studies or two supporting studies with one dissenting study, (3) weak—two or more dissenting trials on a given trigger or no prospective trials at all.

†Studies of the Chinook winds.
‡Studies of monosodium glutamate (MSG)–sensitive patients.
While migraineurs often report a variety of internal and external stimuli that can precipitate a migraine attack, association of these stimuli do not prove causality. Premonitory symptoms can often times be mistaken as triggers. Replication of triggers for experiments can be challenging since many factors contribute to trigger response including prior conditioning, learning, expectation and memory of the response. Also verbal cues as well as location where trigger is being experienced can change the response to the trigger. It is difficult to translate basic science experiments to human subjects. It is also challenging to study a particular trigger in isolation since migraineurs can experience multiple trigger factors simultaneously.
Trigger Factors and Premonitory Features of Migraine Attacks: Summary of Studies

Jelena M. Pavlovic, MD, PhD; Dawn C. Buse, PhD; C. Mark Sollars, MS; Sheryl Haut, MD; Richard B. Lipton, MD
Study Highlights

- Goal of study is not to provide a comprehensive review but to exemplify the methodological issues and opportunities for better understanding of trigger factors and premonitory features.
- Retrospective surveys, diary studies and clinical trials were selected and of the articles selected of each category only few were described to illustrate relevant points.
Retrospective Studies

- Vast majority of retrospective studies used self-report or physician-administered questionnaire to ascertain types and frequency of precipitating factors.
- Prevalence of trigger factors was higher in the clinic-based rather than in the population based studies.
- 15 total retrospective surveys studies selected and mostly studied common triggers already mentioned.
- Reliability of survey data is affected by numerous factors including selection, recall and confirmation bias given self-reporting in clinic-based population.
Diary studies

- Reduce biases introduced from retrospective reporting and allow for rigorous testing of multiple hypotheses.
- Availability of smartphones have made these studies easier to achieve.
- 6 articles selected and divided by electronic and paper approaches.
These studies based on randomized and blinded exposure to potential triggers can provide a powerful and rigorous approach to the study of trigger factors.

In the experimental setting, glyceryl trinitrte, calcium prostaglandin E2 and I2, calcitonin-gene related peptide and pituitary adenylate cyclase-activating polypeptide are triggers in the experimental setting.

Probability of headache after an exposure depends on the timing and dose of the trigger factor.
What Turns on a Migraine? A Systematic Review of Migraine Precipitating Factors

Stephen J. Peroutka
Study Highlights

- Systematic literature review of including both retrospective and prospective studies that determine the prevalence of trigger factors in migraine patients.
- 25 articles selected and most are prospective or retrospective, cross-sectional studies where patients where interviewed directly or self-reported triggers.
- Data of reported incidence taken from each publication and weighted average from each trigger calculated.
- Top 10 migraine precipitating factors analyzed for review.
Conclusions:
- Stress is the most common identified trigger
- Author suggests that common link between all identified trigger factors appears to be an intrinsic difficulty in adapting to internal and external environmental changes

Limitations:
- Very limited information on how articles were selected or how migraine diagnosis made
- Studies were not all similarly designed and there might be bias in reporting of triggers
- Reporting of triggers does not mean that they lead to causality

Table 1: “Top 10” migraine precipitating factors

<table>
<thead>
<tr>
<th>Precipitating factor (general)</th>
<th>% of migraineurs</th>
<th>Total # subjects assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>58</td>
<td>7187</td>
</tr>
<tr>
<td>Auditory</td>
<td>56</td>
<td>397</td>
</tr>
<tr>
<td>Fatigue</td>
<td>43</td>
<td>2577</td>
</tr>
<tr>
<td>Fasting</td>
<td>44</td>
<td>3374</td>
</tr>
<tr>
<td>Hormonal*</td>
<td>44</td>
<td>4461</td>
</tr>
<tr>
<td>Sleep</td>
<td>43</td>
<td>5347</td>
</tr>
<tr>
<td>Weather</td>
<td>39</td>
<td>5527</td>
</tr>
<tr>
<td>Visual</td>
<td>38</td>
<td>5176</td>
</tr>
<tr>
<td>Olfactory</td>
<td>38</td>
<td>5251</td>
</tr>
<tr>
<td>Alcohol</td>
<td>27</td>
<td>3695</td>
</tr>
</tbody>
</table>

*In females only.
The triggers or precipitants of the acute migraine attack

L Kelman
Headache Center of Atlanta, Atlanta, GA, USA

Kelman L. The triggers or precipitants of the acute migraine attack. Cephalalgia 2007; 27:394–402. London. ISSN 0333-1024
Aim of the study was to evaluate and define the triggers of the acute migraine attack.

Retrospective study of patients with migraine with and without aura, probable migraine and chronic migraine in a headache center that were selected for trigger evaluation.

1207 patients were evaluated and 75.9% reported triggers.

Most common triggers: stress (79.7%), hormones in women (65.1%), not eating (57.3%), weather (53.2%), sleep disturbance (49.8%), perfume or smells (43.7%), neck pain (38.4%), lights (38.1%), alcohol (37.8%), smoke (35.7%), sleeping late (32%), heat (30.3%), food (26.9%), exercise (22.1%) and sexual activity (5.2%)

Limitations: single headache clinic and not a population cross-sectional study. Individuals were not always consistent with their triggers from headache to headache.
Methodological Issues in Studying Trigger Factors and Premonitory Features of Migraine

Richard B. Lipton, MD; Jelena M. Pavlovic, MD, PhD; Sheryl R. Haut, MD; Brian M. Grosberg, MD; Dawn C. Buse, PhD
Study Highlights

- Study aims to review methodological approaches to study trigger factors and premonitory features that often precede a migraine attack.
- Self reports are usually common in identifying potential trigger factors but do not provide evidence for a causal relationship.
- Useful data in self reports include headache occurrence, onset and duration, pain intensity, presence of aura or neurological symptoms, associated features, medication use, menstrual cycle, mood, sleep information, diet, caffeine, alcohol and nicotine use, weather and life events.
### Recommendations to further study triggers

<table>
<thead>
<tr>
<th>Design</th>
<th>Strengths</th>
<th>Limitations</th>
<th>Comments/Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveys of beliefs</td>
<td>Assess beliefs about triggers and premonitory features</td>
<td>Influenced by beliefs, recall bias, and potentially by reverse causality</td>
<td>Hypothesis generating</td>
</tr>
<tr>
<td></td>
<td>Study multiple factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paper diary studies</td>
<td>Record candidate exposures and headaches at least daily</td>
<td>With retrospective completion, recall bias</td>
<td>Hypothesis testing but subject to limitations</td>
</tr>
<tr>
<td></td>
<td>Assess the statistical association of exposures to headache occurrence</td>
<td>Burdensome to record daily data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study multiple factors</td>
<td>May not distinguish reverse causality</td>
<td></td>
</tr>
<tr>
<td>Electronic diary studies</td>
<td>Same as paper diaries</td>
<td>Burdensome to record data daily</td>
<td>Rigorous testing of multiple hypotheses</td>
</tr>
<tr>
<td></td>
<td>Time-stamping prevents retrospective recording</td>
<td>May not distinguish causality and reverse causality</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study multiple exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Case cross-over studies</td>
<td>Exposures are recorded in relation to headache days and a sample of non-headache days</td>
<td>Recall bias possible</td>
<td>Hypothesis testing and generating</td>
</tr>
<tr>
<td></td>
<td>Reduce participant burden</td>
<td>May not distinguish causality and reverse causality</td>
<td></td>
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<tr>
<td></td>
<td>Provides time stamping with electronic data capture</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Study multiple exposures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Repeated measures</td>
<td>Links data on triggers from an external source (i.e., weather data) to diary data</td>
<td>Limited to triggers with available data</td>
<td>Hypothesis testing for a specific trigger</td>
</tr>
<tr>
<td>retrospective cohort studies</td>
<td>Efficient, objective exposure assessment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical trials</td>
<td>Randomized exposure to a real or sham trigger factor</td>
<td>Expensive, time consuming</td>
<td>Best approach to reverse causality</td>
</tr>
<tr>
<td></td>
<td>Rigorous control of exposure</td>
<td>Some triggers cannot be studied</td>
<td>Only strong hypotheses should be tested</td>
</tr>
<tr>
<td></td>
<td>Distinguishes causality and reverse causality because exposure is investigator controlled</td>
<td>Study just one exposure at a time</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not suitable for the direct study of premonitory features</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Important effect modifiers may not be taken into account</td>
<td></td>
</tr>
</tbody>
</table>

Designs are briefly presented in the text. "Exposures" include both trigger factors and premonitory features.

Dietary patterns according to headache and migraine status: A cross-sectional study

Pamela M Rist¹,², Julie E Buring¹,² and Tobias Kurth¹,³,⁴
Cross-sectional study among participants in the Women’s Health Study that examined whether low intake of foods that are usually migraine triggers was different among headache patients.

Prior to randomization, women were asked if they ever had a migraine.

Non-migraine and non-headache control group used

From large population of healthy women, authors examined whether low intake of foods commonly recognized as triggers was different with migraine and headache status. They hypothesized that food avoidance would be associated with different types of headaches.

Analysis was limited to particular food items (chocolate, coffee, cottage cheese, bacon, cured meats, among others).

Also data about how often they eat an item was collected.

Prior to randomization, subjects completed a semiquantitative food frequency questionnaire which was assessed for validity and reproducibility.

Odds ratio was calculated for low intake for each food item.
A total of 25,755 women had no headache history
5573 reported non-migraine headache, and 7042 reported migraine
Patients with non-migraine headache and migraine where most likely to have low intake of total alcohol.
Migraineurs with aura were more likely to have low intake of chocolate, ice cream, hot dogs, and processed meats.
Patients with migraine at least once per week were more likely to have low intake of skim/low fat milk and white and red wine
Alcohol, which is a commonly studied trigger, was found to have a low intake in both migraine and non-headache group

Limitations of study:
  › food not assessed as trigger specifically and instead food intake patterns were assessed
  › Cross-sectional study which assessed only migraine status and food intake, which does not allow for temporal association between migraine status, migraine frequency and food intake
  › Migraine and headache status self-reported which allows for misclassification of migraine
  › All participants were female health professionals which may not generalize to other populations
How should we counsel patients?

- Patients with infrequent and no-n debilitating headaches likely do not need to modify trigger factors.
- Patients with more than 4-5 migraine days per month, with debilitating headaches and migraines refractory to abortive medications should also be counseled on trigger avoidance.
- It is nearly impossible to have patients exclude all potential triggers.
- Patients should be usually encouraged to keep a diary but however it is difficult to keep track of triggers and to determine if a particular trigger leads to a migraine or worsened an attack.
- Well documented lifestyle modifications that patients should be counseled on include:
  - Limit caffeine to < 2 cups per day
  - Regular sleep hygiene of at least 8 hours
  - Eat regular meals, protein at breakfast, avoid fasting
  - Minimize stress, exercise, practice relaxation techniques
  - Avoid bright or flickering lights