Curr Pain Headache Rep (2014) 18:455
DOI 10.1007/s11916-014-0455-y

MIGRAINE (R COWAN, SECTION EDITOR)

# Sufficiency and Necessity in Migraine: How do we Figure Out if Triggers are Absolute or Partial and, if Partial, Additive or Potentiating?

**Egilius L. H. Spierings · Stephen Donoghue · Alec Mian · Christian Wöber**

Published online: 28 August 2014


**Abstract** Migraine is, to a great extent, a genetically determined disorder and once it has manifested itself, it generally continues for years if not for decades. While the migraine is active, headaches can seemingly occur spontaneously but are often reportedly precipitated by events or factors, known as migraine triggers, the interplay of which is the topic of this paper. Among migraine triggers, the menstrual cycle is an important one that probably accounts for much of the excess of migraine in women compared with men. Much has also been written about stress as a trigger of migraine, with headache occurring after rather than during stress, when relaxation occurs. Stress is also 1 of the 4 most often acknowledged headache triggers in general, the others being fatigue, not eating on time, and lack of sleep. Singularly, the triggers are generally necessary but not sufficient, ie, not powerful enough to bring on headache by themselves and, hence, compounding of those triggers is usually required. There is evidence to suggest that the premenstrual phase has a magnifying effect on the stress-headache interaction. The same is true for low-sleep duration with the (predictive) model fitting best when stress and low-sleep duration are considered additive. Menstruation has been identified as possibly the only absolute trigger of headache that is both necessary and sufficient. The scientific study of migraine triggers requires knowledge not just of how often in an individual a trigger is followed by migraine headache but also of how often it is not. Having identified trigger-headache associations, it needs to be determined which triggers are causative in the individual, either singly or in combination with others. This requires running an experiment with the individual that involves behavioral intervention to change exposure to a given trigger and determine whether that improves migraine. The ubiquitous adoption of the smart phone as a personal-data entry device, along with the possibility of bringing the results of sophisticated statistical analysis into the hands of patients and physicians, may well provide us with an important set of tools that will finally allow the unravelling of the age-old migraine-trigger puzzle.

**Keywords** Migraine · Trigger · Menstruation · Stress · Estrogen · Caffeine · Alcohol · Fatigue · Lack of sleep · Oversleeping · Time-series relation · Aura · Prodrome

This article is part of the Topical Collection on *Migraine*

E. L. H. Spierings
Division of Craniofacial Pain, Tufts University School of Dental Medicine, Boston, MA, USA

E. L. H. Spierings
Headache and Face Pain Program, Department of Neurology, Tufts Medical Center, Boston, MA, USA

E. L. H. Spierings (✉)
Tufts University School of Dental Medicine, One Kneeland Street, Boston, MA 02111, USA
e-mail: Egilius.Spierings@Tufts.edu

S. Donoghue · A. Mian
Curelator Incorporated, Cambridge, MA, USA

C. Wöber
Department of Neurology, Medical University of Vienna, Vienna, Austria

## Introduction

Migraine is, to a great extent, a genetically determined disorder with an onset, accordingly, often in childhood. Childhood migraine is typically associated with vomiting, which at the same time tends to provide headache relief. Sleep often provides the ultimate relief of headache in both childhood and adulthood, with the headache often resolved by a daytime nap

in children and generally requiring overnight sleep in adults. Beyond childhood, migraine onset is often brought on by particular events, for example, migraine onset in almost 30 % of women is at the time of menarche in puberty [1]. Interestingly, menarche at age 12 or younger is associated with a higher prevalence of headache and migraine than menarche over age 12, also when adjusted for important cofounders, such as age, body mass index, and oral-contraceptive use [2]. In adolescence and early adulthood, the use of an estrogen-containing contraceptive can initiate migraine as can, in adulthood, pregnancy, although with the latter the onset occurs more commonly after pregnancy/nursing than during pregnancy. During pregnancy, especially in the second and third trimesters, migraine tends to improve.

Menarche, the use of an estrogen-containing contraceptive, and pregnancy are of course exclusively female events, causing postpubertal women to suffer from migraine 2–3 times more commonly than men, whereas in childhood boys slightly outnumber girls. The circumstances of headache onset, when it occurs in adulthood, ie, after menarche in women, were looked at in a study of 566 patients attending a headache practice [3]. Of these patients, almost 40 % reported a specific event related to the onset of their headaches: Head, neck, or back injury in 29.0 %; stress in 17.2 %; pregnancy in 12.2 %; oral-contraceptive use in 5.4 %; surgery in 5.0 %; flu-like illness in 4.5 %; illness in 4.1 %; spinal tap in 4.1 %; estrogen-replacement therapy in 3.2 %; and dental procedure in 3.2 %. In the remaining 60 %, the patients were not able to mention a specific initiating event.

Once manifested, migraine generally continues for years if not for decades, sometimes lasting until the end of life, although often mitigated from a headache perspective with the advancement of age. While the migraine is active, varying in frequency from occasionally to several times per week, headaches can seemingly occur spontaneously but are often reportedly precipitated by events or factors, known as migraine triggers, the interplay of which is the topic of this paper.

Of the triggers noted in the literature, the menstrual cycle is an important one that probably accounts for much of the excess of migraine in women compared with men. Women are particularly vulnerable to migraine perimenstrually but also, although often to a lesser extent, mid-cycle at the time of ovulation. Headaches triggered by the menstrual cycle tend to be severe, disabling, and relatively long-lasting, often continuing for days. In a relatively recent study of 38 women with menstrually-related migraine, daily early-morning urine samples were collected for measurement of estrone-3-glucuronide and pregnanediol-3-glucuronide, urinary metabolites of estradiol and progesterone, respectively [4]. The data were shifted 1 day for comparison with headache occurrence recorded on daily diary cards, to account for the fact that the early-morning urine measurements reflect serum hormone levels 12–24 hours earlier. The menstrual cycle was divided into phases of rising estrogen and those of falling estrogen and migraine occurrence was found to be statistically significantly lower during the former and higher during the latter. Most migraine headaches were observed to occur between 3 days before menstruation and 4 days into menstruation.

Other common chemicals are also believed to cause headache, including caffeine, either in caffeine-containing beverages or in caffeine-containing (headache) medications, sometimes upon introduction into the system but to a greater extent upon withdrawal [5]. Alcoholic drinks tend to bring on headache as well but with a certain delay, although it is not clear whether this is (always) due to the alcohol or due to other implicated chemicals, such as congeners and biogenic amines. Biogenic amines are also present in dietary products, such as aged cheese and dark chocolate, which are food products often avoided by individuals with migraine because of their potential headache-triggering properties.

Much has been written about stress as a trigger of migraine headaches and 3 patterns have been described [6]. Following stress in the afternoon, migraine headache tends to develop in the evening or during the night, when the mind and body relax. When stress extends into the evening, the migraine patient wakes up the next morning feeling tired and develops headache during the course of the morning. The stress in the evening possibly results from tension, which in turn leads to fatigue upon awaking. The situation is different when the tension seems to have more of an arousing effect, making the patient particularly alert. Then the patient feels stressed the next morning and becomes tense and irritable, which is followed by headache in the evening.

Stress or tension and fatigue were among the 4 most often acknowledged triggers of headache in a study of 28 patients with migraine, the other 2 being not eating on time and lack of sleep [7]. These 4 triggers were acknowledged by 74 %–84 % of the migraine patients, which was about the same in the 17 patients with tension-type headache studied, suggesting that these are general and nonspecific headache triggers. When genetically predisposed to migraine, the triggers bring on migraine headache; otherwise, tension-type headache will be the consequence. No specific triggers were identified for tension-type headache but the 4 additional triggers that differentiated migraine from tension-type headache were weather, odors, tobacco smoke, and bright light.

## The Migraine Firecracker: Necessity and Sufficiency

Clinically, it seems that the chemical triggers mentioned, particularly estrogen and caffeine but possibly also alcohol, are potent enough to act on their own, ie, they are necessary and sufficient to cause migraine headache. Stress may be in the same category if followed by relaxation, allowing the migraine pathophysiology to express itself [8]. Alternatively,

stress may be necessary but not sufficient and needs fatigue, irritability, or other subsequent and additive or potentiating triggers to generate a migraine headache. John R. Graham, a mentor of the first author, promulgated the additive view on migraine triggers, as illustrated by Fig. 1, depicting the "migraine firecracker" [9]. He wrote: "Thus, the migraine patient may be compared with a highly explosive firecracker, which can be set off easily by any one of these naughty boys, the stimuli from the external or physiologic or psychologic environment, to produce the migraine 'explosion' or attack…One alone may not produce the migraine attack when combinations will. Thus, alcohol on a hot day, or the smell of paint plus the noise of construction may league together to push the sensitive subject into an attack. In the same way, a number of common stimuli from the physical and emotional environment may, singly, or in pairs, operate to produce headache. A day shopping, without lunch, at the time of the menstrual cycle is a good example; or loss of sleep and excessive nicotine and prolonged mental strain make an effective combination."

In summary, migraine triggers are intrinsic or extrinsic factors that interact with susceptible individuals to cause migraine headache. They may be either necessary and sufficient or necessary and insufficient, the latter, at least in theory, requiring additional, additive or potentiating triggers. What makes individuals susceptible to migraine is probably, to a great extent, genetic but this is not the topic of this paper. Nor is the identification of the triggering events, which can be and often is challenging, or the nature of the interaction between triggers and individuals, ie, the biology of triggered migraine headaches. Instead, this paper focusses on the interaction between the triggers and the individuals per se and how the necessity and sufficiency of potentially interacting triggers can be studied scientifically.

## Partial or Absolute Nature of Triggers

An indication of whether single triggers are both necessary and sufficient is reflected by the consistency with which they provoke migraine headaches, as determined in a study of 120 patients with migraine or tension-type headache [10]. With regard to their acknowledged triggers, patients were asked on the basis of their personal experience whether they brought on headache always, ie, consistently, or sometimes, ie, occasionally. Of the 15 most common triggers acknowledged, ie, menstruation, weather, stress, red wine, smoking, hunger, alcohol, skipping meals, noise, change in sleeping habits, glare, relaxation after stress, exhaustion, odors, and physical activity, only menstruation was statistically significantly more often indicated as a consistent rather than an occasional trigger. This suggests that, singularly, the triggers are generally necessary but not sufficient, ie, not powerful enough to bring on headache by themselves. Hence, compounding of those triggers is usually required to bring on migraine headache.

## Additive or Potentiating Nature of Triggers

In a study of 12 menstruating migraineurs and 12 age-matched, nonheadache female controls, excluding those on birth control pills as well as those with pure menstrual migraine, it was found that stress coping varied across the menstrual cycle similarly in both groups of women [11]. In the women with migraine, headache activity was statistically significantly increased premenstrually, despite the exclusion of women with pure menstrual migraine, while stress was not found to vary by phase of the menstrual cycle. However, it was only premenstrually that headache and stress were statistically

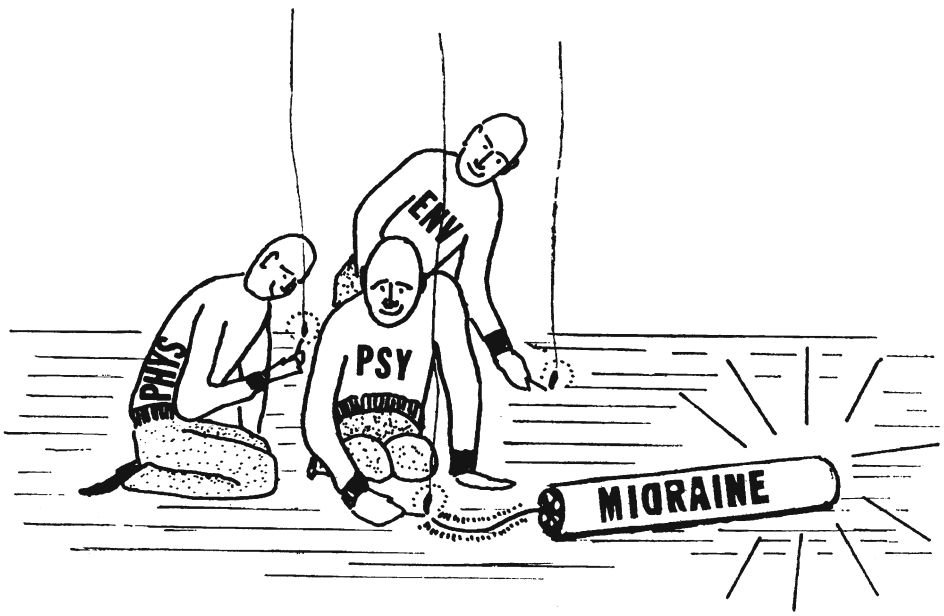


**Fig. 1** The migraine firecracker. Reproduced from Graham JR, Michigan Med. 1965;650–4

significantly correlated, suggesting a magnifying effect of the premenstrual phase on the stress-headache interaction.

In a study of the interaction of the effects of stress and sleep duration in 33 patients with chronic migraine and 22 with chronic tension-type headache, the time-series relations between stress, sleep duration, and headache were determined by applying a series of linear mixed models, generating the following observations [12••].

1. High stress yesterday and today predicts very high headache activity today;
2. Low stress yesterday and today predicts low headache activity today;
3. Low stress yesterday and high stress today also predicts low headache activity today;
4. High stress yesterday and low stress today predicts high headache activity today.

The conclusion regarding the stress-headache relation was that headache precipitation needs at least 2 consecutive days of stress (observations #1 and #3) and that headache is also likely to occur during let-down after stress (observation #4). The latter was recently confirmed in a diary study of 17 migraine patients who recorded stress level and migraine occurrence on a daily basis for 12 weeks [13].

Regarding sleep duration and headache, the following observations were made:

1. Low sleep duration (<4 hours) yesterday and today predicts very high headache activity today;
2. Low sleep duration yesterday and high sleep duration today also predicts high headache activity today;
3. Approximately 8 hours of sleep on consecutive days predicts low headache activity today.

The conclusion regarding the sleep duration-headache relation was that headache precipitation needs at least 2 consecutive days of sleep deprivation (observation #1) and that headache is also likely to occur with oversleeping (observation #2). Looking at stress and sleep duration combined, low stress, and low sleep-duration risk scores were associated with the lowest headache activity today and the most headache activity today occurred when both were high, with the (predictive) model fitting best when the stress and sleep-duration scores were considered additive.

## Interaction Between Triggers and Individuals

If all single triggers were both necessary and sufficient, ie, absolute, and this occurred regardless of the individual, and if the intensity and duration of the exposure were irrelevant, and if the triggered headaches would come on instantaneously, this paper would be superfluous and migraine would not continue to be such a significant medical and social concern. It would be easy for patients to identify the triggers relevant for them and for physicians to guide patients avoid or to learn patients cope with their triggers in order to ameliorate their condition [14]. However, none of this is true and patients and physicians alike continue to struggle with this approach to migraine treatment, often to the extent of giving up after much time and effort has been put into trying to identify the individual's triggers. If we look at the factors complicating the trigger-individual interaction resulting in migraine headache, they can be broken down as follows:

(1) The relative power of the triggers combined with intensity and exposure;
(2) The susceptibility of the individuals in terms of trait and state;
(3) The time interval between exposure and ensuing migraine headache.

The study by Wöber et al [15] identified menstruation as possibly the only absolute headache trigger that is both necessary and sufficient, with all the other ones studied definitely being partial, ie, necessary but not sufficient. However, menstruation is not a trigger in all menstruating women with migraine, although when it is, it tends to trigger migraine headaches consistently. What determines whether or not menstruation is a trigger in a particular menstruating woman is not known and could be related to the individual's migraine susceptibility or to particular quantitative or qualitative features of the menstruation-related hormonal changes, assuming that the underlying mechanism is, indeed, hormonal. In regard to the latter, it has been suggested that the issue is an imbalance between the estrogen and progesterone hormones (qualitative) [16] or an overproduction of estrogen hormones (quantitative) [4]. An argument in favor of the latter view is that headache is a dose-dependent side effect of an exogenous estrogen, ethinyl estradiol [17].

Regarding intensity and duration of exposure, the study by Houle et al [12••] shows these aspects of exposure to be important at least with regard to the common triggers of stress and lack of sleep. Susceptibility in terms of trait is, as mentioned, not covered by this paper but susceptibility in terms of state is important to bring into the equation. The best example of this is the state of relaxation, as described by Spierings et al [6] and Houle et al [12••], and explained in physiological terms by Spierings [8]. The occurrence of migraine headache after rather than during stress, ie, when relaxation occurs, illustrates the importance of the time factor as well; this is also well known for alcohol and other vasodilators, including nitroglycerine and calcitonin gene-related peptide, which typically cause migraine headache after a certain delay.

As most if not all migraine triggers are necessary but not sufficient, although certainly varying in relative strength, compounding is generally required as so nicely illustrated by Graham's conspiring naughty boys. This presents a challenge for trigger identification. The time factor is another challenge, which may be worse because little is known about which triggers it affects and what the time interval is for the various triggers so affected. Collecting patient data to study timed delays is challenging: having patients input large numbers of putative triggers every day at time intervals of less than 24 hours for an extended period of time may be too demanding. Good compliance may be expected with daily diary entries once per day but patients are less likely to be willing to enter data twice per day or more often. The necessity to record the exact time, duration, and intensity of exposure also varies from trigger to trigger. For menstruation, the date is probably sufficient; sleep duration and sleep quality may also not require further temporal specification. However, regarding, eg, bright light, odors, or stress, the consequences may be different for short-lasting, intense exposure compared with prolonged exposure at low intensity.

A third challenge is that migraine headaches, while rarely preceded by (neurologic) aura symptoms, are often preceded by so-called prodromes, which are ill-defined, non-neurologic symptoms that can precede migraine headaches by hours. Such prodromes include sensory sensitivity (difficulty reading, blurred vision, sound sensitivity, dizziness, smell sensitivity, sensitive skin), pain/stiffness (pain in forehead or back of the head, stiff or painful shoulders, pain in the neck, stiff neck), fatigue (strained eyes, feeling weary, rickety, tired, exhausted, lifeless, sleepy), good cognitive functioning (things in order, head clear, alert, able to concentrate, competent, efficient), positive affect (inspired, strong, relaxed, contend, pleased), negative affect (tense, dreary, annoyed, worried, sad, lonely, angry), effort (working hard, strained, not at ease, busy, much expected, exerting very much, thinking hard), and stress (something unpleasant, conflict, problem couldn't solve, things not going my way).

A study looking at the above prodromes in the 72 hours preceding migraine headache found sensory sensitivity, pain/stiffness, and fatigue to be statistically significantly increased within the 12 hours before migraine headache as well as a tendency for increased negative affect in the same time window [18]. These prodromes may harbor triggers but, on the other hand, may be confused with triggers or triggers may be confused with them. An example is photophobia and/or blurred vision preceding migraine headache, which is sometimes erroneously diagnosed as migraine with aura, while the symptoms are neither neurologic nor limited in duration as aura symptoms are. The trigger that these prodromal symptoms may be harboring is eyestrain, a relatively poorly investigated headache trigger [19].

## Scientific N-of-1 Approach to Dissecting Migraine Triggers

In the scientific study of migraine triggers, examination of an individual's headache activity over time can, at least in theory, establish a background headache probability against which the triggers can be studied [20]. The consistency of repeated pairing in time of trigger and headache can provide an assessment of the headache-related causal strength of the trigger. Different strengths for different triggers are likely to be found, generating an estimate of the relative power of triggers in bringing on migraine headache. The relative strength, thus found for the premenstrual phase of the menstrual cycle bringing on migraine headache, possibly the only close to absolute migraine trigger, could be used to "calibrate" the other triggers identified, which then may provide an opportunity to determine whether the synergy of triggers is additive or potentiating.

The challenges, therefore, are first to find the associations between putative triggers and the occurrence of migraine headaches in a given individual and, secondly, to establish that the triggers do, indeed, contribute to the occurrence of migraine headaches. In order to find associations, it is important to realize that it requires knowledge not just of how often a trigger is followed by migraine headache but also of how often it is not, ie, how often the trigger is not followed by migraine headache. We can then apply statistical models that allow for the temporal relations of triggers and headaches to determine which triggers increase the risk of headache and which do not. Hence, we need daily information about the individual (sleep, stress, diet, etc) and other factors that may be triggers (eg, weather [21, 22]), and we need this information in a reliable and readily analyzable format.

Having identified trigger-headache associations, we then need to determine which triggers are causative in the individual, either singly or in combination with others. We can do this by running an experiment with the individual that involves behavioral intervention to change exposure to a given trigger (eg, do not drink red wine) and determine whether that improves migraine (ie, results in fewer headaches). It may be necessary to test changing combinations of triggers rather than single triggers because 1 trigger alone may not have a powerful enough effect to be detectable in such an N-of-1 study. Again reliable daily information is needed from the individual and then, over time, the relevant (strongest) triggers and/or combinations of triggers can be determined for the individual and, potentially, beneficial lifestyle changes can be proposed.

Obtaining such trigger-headache information from a large number of people with migraine should allow us to better understand which triggers are common and/or strong and which ones may only become important when they act together. It may even be possible to identify types of people who have migraine and share a cluster of common triggers. Such

population data could also be used to further refine the individual's trigger-identification and trigger-testing processes.

In summary, causative trigger identification and subsequent behavioral changes have the potential to benefit people with migraine. However, it is only achievable if reliable daily information is collected, if the analysis is performed using appropriate statistical modelling, and if trigger-modification testing is executed to prove causality.

An example of a scientific approach to the identification of migraine triggers to benefit people with migraine is the one developed by Curelator Incorporated, Cambridge, Massachusetts, USA. It is a novel, web-based platform that aims to guide users with migraine to identify associations between triggers and headaches and then test behavioral modifications to determine if a putative migraine trigger is truly causative. The platform, called Curelator Headache, includes a website for education, advice, secure registration, and entry of medical information, including headache history. This then links to, and individually customizes for each individual, an application for use on an internet terminal, such as smartphone, tablet device, laptop, or other kind of computer, which acts as the primary data-entry interface. In a simple-to-use way daily trigger, headache, and other information are entered by the user, along with other health information that the individual wishes to track. The data are downloaded to a secure database and a proprietary analytical engine using statistical modelling analyses the data in real time. When enough data has been entered, Curelator Headache determines associations between single or combinations of triggers and the occurrence of migraine headaches.

Significant associations are displayed to the individual user and behavioral-change tests are proposed to modify the trigger exposure to determine the effect on the frequency of migraine headaches. This may involve avoiding or modifying a trigger or combinations of triggers, potentially allowing triggers to be confirmed as causative, although it may also show that the trigger-exposure modification does not impact migraine. The aim, through iterative testing, is to identify important triggers in individuals and provide them with behavior modifications that improve their migraine condition. Eventual use of Curelator Headache by thousands of people with migraine is expected to result in a large database that can be mined for information about proven triggers, their (temporal) relations to migraine headaches, and how they behave in relation to each other in terms of additive or potentiating effects.

The ubiquitous adoption of the smart phone as a personal-data entry device, along with the possibility of bringing the results of sophisticated statistical analysis into the hands of patients and physicians, may well provide us with an important set of tools that will finally allow the unravelling of the age-old puzzle: which triggers are necessary and sufficient (ie, absolute) vs which triggers are necessary but insufficient (ie, partial) in provoking migraine headache and in which individuals.

**Compliance with Ethics Guidelines**

**Conflict of Interest** Stephen Donoghue and Alec Mian are employees of Curelator Incorporated, Cambridge, Massachusetts, USA. Egilius L. H. Speirings is a consultant for Curelator Incorporated and Christian Wöber reports payment from Curelator to his institution for the use of data on migraine triggers. He is also a consultant to Curelator.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

## References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance


1. Spierings ELH. Onset and relief of headache in patients attending a headache practice: a survey. Headache Quart. 1996;7:324–5.
2. Aegidius KL, Zwart J-A, Hagen K, Dyb G, Holmen TL, Stovner LJ. Increased headache prevalence in female adolescents and adult women with early menarche. The Head-HUNT Studies. Eur J Neurol. 2011;18:321–8.
3. Karpouzis KM, Spierings ELH. Circumstances of onset of chronic headache in patients attending a specialty practice. Headache. 1999;39:317–20.
4. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Incidence of migraine relative to menstrual cycle phases of rising and falling estrogen. Neurology. 2006;67:2154–8.
5. Spierings ELH. Headache caused by medications and chemicals. Headache Quart Curr Treat Res. 1992;3:403–7.
6. Spierings ELH, Sorbi M, Maassen GH, Honkoop PC. Psychophysical precedents of migraine in relation to the time of onset of the headache: the migraine time line. Headache. 1997;37:217–20.
7. Spierings ELH, Ranke AH, Honkoop PC. Precipitating and aggravating factors of migraine vs tension-type headache. Headache. 2001;41:554–8.
8. Spierings ELH. The physiology and biochemistry of stress in relation to headache. In: Adler CS, Adler SM, Packard RC, editors. Psychiatric aspects of headache. Baltimore: Williams & Wilkins; 1987. p. 237–53.
9. Graham JR. The treatment of migraine. Michigan Med. 1965;64: 650–4.
10. Wöber C, Holzhammer J, Zeitlhofer J, Wessely P, Wöber-Bingöl C. Trigger factors of migraine and tension-type headache: experience and knowledge of the patients. J Headache Pain. 2006;7:188–95.
11. Holm JE, Bury L, Suda KT. The relationship between stress, headache, and the menstrual cycle in young female migraineurs. Headache. 1996;36:531–7.
12.•• Houle TT, Butschek RA, Turner DP, Smitherman TA, Rains JC, Penzien DB. Stress and sleep duration predict headache severity in chronic headache sufferers. Pain. 2012;153:2432–40. *This study evaluated the time-series relationships between stress, sleep duration, and headache pain among patients with chronic headache.*
13. Lipton RB, Buse DC, Hall CB, Tennen H, DeFreitas TA, Borkowski TM, et al. Reduction in perceived stress as migraine trigger. Testing the "let-down headache" hypothesis. Neurology. 2014;82:1395–401.
14. Martin PR. Managing headache triggers: think "coping" not "avoidance". Cephalalgia. 2010;30:634–7.

15. Wöber C, Brannath W, Schmidt K, Kapitan M, Rudel E, Wessely P, et al. Prospective analysis of factors related to migraine attacks: the PAMINA study. Cephalalgia. 2007;27:304–14.
16. Dalton K. The premenstrual syndrome and progesterone therapy. London: William Heinemann Medical Books; 1977.
17. Preston SN. A report of a collaborative dose-response clinical study using decreasing doses of combination oral contraceptives. Contraception. 1972;6:17–35.
18. Houtveen JH, Sorbi MJ. Prodromal functioning of migraine patients relative to their interictal state—an ecological momentary assessment study. PLoS One. 2013;8:e72827.
19. Vincent AJP, Spierings ELH, Messinger HB. A controlled study of visual symptoms and eye strain factors in chronic headache. Headache. 1989;29:523–7.
20. Turner DP, Smitherman TA, Martin VT, Penzien DB, Houle TT. Causality and headache triggers. Headache. 2013;53:628–35.
21. Zebenholzer K, Rudel E, Frantal S, Brannath W, Schmidt K, Wöber-Bingöl C, et al. Migraine and weather: a prospective diary-based analysis. Cephalalgia. 2011;31:391–400.
22. Becker WJ. Weather and migraine: can so many patients be wrong? Cephalalgia. 2011;31:387–90.