Dialogs with Headache Patients

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Edited by

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Cambridge
Scholars
Publishing

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This book first published 2022

Cambridge Scholars Publishing

Lady Stephenson Library, Newcastle upon Tyne, NE6 2PA, UK

British Library Cataloguing in Publication Data
A catalogue record for this book is available from the British Library

ISBN (10): 1-5275-8726-6
ISBN (13): 978-1-5275-8726-7

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PREFACE

CONVERSATIONS WITH HEADACHE PATIENTS

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ROBERT G. KANIECKI, MD

As educators in the field of headache medicine we are commonly asked, “how do you explain that to a patient?” The “that” may involve issues surrounding diagnosis, testing, different treatment options, or even the basic explanations of the physiology behind the headache. Some patients may need to be reassured; others desire to learn more.

Patients often enter the headache specialist’s office with a set of common questions. Health care providers are expected to be able to provide answers that are thorough and understandable. This book provides responses to patient concerns using a clear, conversational format. Providers and patients alike will benefit from this broad compilation of questions and answers. Some may be raised during the office encounter, while others may have been neglected and only considered afterwards. This text articulates many different aspects of patient’s common concerns and can empower the patient to implement many solutions themselves.

The most common type of headache is a tension type headache; yet, by definition, these are not disabling and rarely prompt a visit to a health care provider. Migraine is by far the most common headache that prompts a visit, which is why so many of the conversations are dedicated to migraine-related issues. Since most migraineurs are women of child-bearing years, several sections are devoted to headaches and reproductive issues. Many other specific patient subgroups – children, transgenders, specific religious denominations – have different needs and different questions which are addressed in detail.

We invited experts with experience in clinical headache settings and asked them to provide their tips and insights. Bringing them together and editing their sections has been enjoyable and informative. There is much to learn within these pages, as none of us have “all the answers.”

MIGRAINE IN A TRANSGENDER INDIVIDUAL

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I identify as transgender, and I just started on estrogen gender-affirming hormone therapy (GAHT). My migraine attacks have changed, and it seems like they are happening more frequently. Why is that?

There is a lot we know and don't know about how hormones affect the brain and the experience of migraine. We know that hormone fluctuations can trigger migraine in cisgender women especially during the menstrual cycle. Some women experience a migraine attack as estrogen levels drop during the cycle; it is that "delta", the change in the estrogen level, that can trigger pain. In other studies, at the basic hormone level, it appears that estrogen is pro-inflammatory, and high levels of estrogen can increase the likelihood of the chemical and electrical changes in the brain that cause migraine. Estrogen change or administration can also lead to aura, which some people with migraine have, but not all.

We don't have specific data in transgender individuals, but it has been suggested that hormones can affect the frequency of migraine attacks, sometimes for the better and sometimes for the worse. Since it seems estrogen can be pro-excitatory in the brain, transgender women on estrogen may notice an uptick in their migraine frequency when first starting on estrogen. The same possibility can happen in cisgender women on estrogen-containing birth control. One study showed that even non-migraine pain, such as musculoskeletal pain, may be increased in transgender women when they start estrogen.

I have migraines, but I have never had aura before. Since I am on estrogen, will I get an aura?

Since estrogen has been shown to increase the likelihood of aura, there is a possibility you may experience new aura when starting on estrogen or continuing on estrogen. Some examples of aura patients have described include seeing squiggly lines or zig-zags, rainbow shimmery arches of light, or black and white dots or spots in their vision. Usually, the aura comes right before a migraine headache, and can last for minutes to an hour, but for some people the aura happens without the headache. Not everyone on estrogen has aura though, so there is also a possibility you will not get aura. Each individual responds to hormone therapy differently, so it is important to monitor for new symptoms when starting on GAHT and follow up with your doctor if you do.

So, do all gender-affirming hormone therapies cause changes in migraine headaches?

Not necessarily. While some basic studies suggest estrogen is pro-inflammatory, other studies imply that testosterone can reduce pain processing. Some people who start on testosterone therapy may notice an improvement in migraine frequency or severity, while others, because hormone levels are changing, may notice an increase in attacks. Some people on GAHT experience no change in their migraine attacks at all. Each individual is different, and their response to GAHT can be different, so it is important to monitor headache frequency and attacks as one starts on hormone therapy.

Given we know that is the cycling or fluctuation in the level of hormones that can be triggers for migraine, it is possible that once transgender people are on stable hormone therapy, that that stability in hormone levels may lead to an improved headache frequency over the long term. What that means is, if you are in the beginning of your hormone therapy, your headaches may go up and down in terms of how often they are happening, but once your dosing regimen has been the same for a while and there have been no changes, your headache attacks may stabilize as well, and you will not notice as much of a roller-coaster ride with your frequency.

Do I need to stop hormone therapy because of my migraine attacks?

No! Transgender people with migraine do not have to choose between continuing hormone therapy and managing their migraines. Both can happen at the same time, and they should. Again, often when people are stable on gender-affirming hormone therapy and the doses do not change, migraine frequency can level off. Treatment for migraine should help support the continuation of hormone therapy, so long as the medications used to treat migraine do not interact with the hormones being given. Your endocrinologist and headache medicine specialist can work together to help monitor your hormones and your migraines.

What can I do to treat my migraines while I stay on estrogen?

There are many acute and preventive therapies that are available to treat migraine. Regardless of medication, one of the mainstays of migraine prevention is lifestyle modification. People with migraine, regardless of their gender identity, are encouraged to have a balanced diet and not miss meals, stay well hydrated, use less than 200mg of caffeine daily at the same amounts at the same time, try to keep active and exercise at least two to three times a week where possible. Getting adequate sleep, at sleeping the same hours each day, and stress reduction are also important. Minimizing triggers wherever possible will also help to keep migraine frequency at bay.

There are many oral and non-oral preventive treatment options to consider for migraine, as well as many acute therapies that come in a number of formulations. Nonpharmacologic options such as neuromodulation, nerve blocks, physical therapy, and behavioral therapies (such as biofeedback and cognitive behavioral therapy) are also excellent treatment options and should be considered. Choosing the right migraine therapy is best done together with your physician.

Will gender-affirming surgery affect my headaches also?

We do not have any data on gender-affirming surgeries, like “top” surgery, and migraine – but they do not seem to affect migraine frequency in a negative way. Some patients will experience a slight flurry of headaches immediately post-operatively, likely due to the stress of the surgery itself, not eating before the procedure, etc. But afterwards, many patients find their migraine frequency may improve. This may be due to a lot of factors, but often it is related to improvement in or alleviation of gender dysphoria.

Are there any treatments or medications for migraine I should avoid since I am on gender-affirming hormone therapy?

There are no specific studies on the traditional or newer therapies for migraine in gender-diverse patients on GAHT. However, based on our understanding of how hormones are metabolized, there are a handful of medications that you may want to consider avoiding until better data is available.

Estrogen and testosterone are metabolized through a specific pathway in the liver, and a couple of medications used to treat migraine are also metabolized through that same pathway. It has been suggested to avoid these medications as there is a possibility the medications may interact. For people on testosterone, some oral preventive medications like valproic acid and zonisamide can affect levels of testosterone so these should be used with caution. For those on estrogen, topiramate and carbamazepine/ oxcarbazepine can affect levels as well, so if you are on any of these medications, your hormone levels should be monitored regularly.

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HOW IS IT POSSIBLE FOR ONE PERSON TO HAVE SO MANY DIFFERENT HEADACHES?

ROGER K. CADY, MD
KATHLEEN FARMER-CADY, PSYD

I'm confused. How can I have so many different headaches?

At 12, my headaches began. A couple of years later, in the middle of allergy season, my headaches were interfering with my schoolwork. I visited my Primary Care doctor who pinpointed my problem as sinus headaches.

Over the next several years, after several antihistamines, desensitization shots, and steroids, I made an appointment with an ENT physician. He identified a bone spur in my nose and recommended and conducted surgery. My headaches never resolved but they improved for several months in the late Fall and Winter but worsened in the Spring and early Summer.

Later a friend whose mother was a physician suggested I seek help from a neurologist. I was diagnosed as having migraine. She prescribed a triptan which helped but warned that I should only use this medicine when I was certain I was having a migraine. She cautioned that triptans constricted blood vessels and could cause heart attacks by pinching off the blood flow in my heart. Because the medicine often produced tingling and sometimes slight chest pressure, I was careful to take it only when I really needed it. If the triptan failed to work, the headache sent me to bed for days.

At 19, I had the most severe headache of my life. I sought help at the emergency room. The doctor thought a blood vessel had broken inside my head. He ordered a CT scan and spinal tap. The studies were normal, but he diagnosed my very severe headaches as cluster headache. He explained that cluster was the worst pain a person could have and were called suicide headaches--not what I needed to hear.

From then on, I sought relief from other physicians, counselors, and psychiatrists. Each had a different message for me. I was told I was under too much stress and had depression and anxiety, bipolar disorder, fibromyalgia, and even bad bacteria in my intestines. I saw massage therapists, chiropractic doctors, nutritionists, and a holistic doctor. Lots of new diagnoses each with different solutions and all promising a cure for my headaches.

Years later, I was having headaches all the time, almost every day. Another healthcare provider (HCP) told me I had yet another kind of headache, 'chronic daily headache.' He explained that some days the headaches were tension headache but other days they were migraine. He called these 'mixed headaches' and 'tension/vascular headaches' because they involved both the muscles and blood vessels. The tension headache was due to my poor posture that resulted from holding my head still for long periods to avoid head movement when I had headaches.

A colleague at work recommended another neurologist who had helped her a lot. This neurologist diagnosed me with chronic migraine that she described as a new diagnosis that replaced the diagnosis of chronic daily headache. She suggested that instead of classifying the headaches as either migraine or tension headaches, I should think of all the headaches as being either migraine or headaches that will become migraine if I don’t treat them as soon as the headache begins.

She was the first to put me on prevention medication. It was supposed to prevent headaches and also help me lose weight but all it did was made me forget people's names, so I was switched to another medicine to prevent migraine which I take daily to this day even though it doesn’t seem to be helping. She suggested a new triptan and gave me high doses of an over-the-counter medicine to treat minor headaches as soon as they began. When all else failed, I was to rely on a pain killer for rescue so I could stay out of the emergency room.

Two years later, I was diagnosed as having medication overuse headache, meaning I was taking medication too often and my taking too much medication was now the cause of my headaches. That didn’t make any sense to me.

I was referred to you because you are a headache specialist and I need help. I hope you will give me more than just another diagnosis.

I hope so too. I've had an opportunity to carefully review your medical history. After an examination, you and I will begin by discussing the first question you asked me, "How can I have so many different headaches?"

Thank you for the opportunity to help you manage your headache. I want to let you know from the start I don't have all the answers, but I believe if we work together from a clean slate, we'll get close to finding most of the answers you're looking for. The key for us to accomplish this is working together as partners. You are the expert of your headaches and experience. I am trained in medicine and headache diseases. Together I think we can discover solutions that help you control headaches.

Your story exemplifies the "spectrum of headache symptoms" that is often experienced over time by people with a primary headache disorder. Headaches are great masqueraders and depending on life circumstances and what might have triggered a specific headache there can be a wide range of different symptoms a person might experience. Headaches can range from being mild with slight discomfort to excruciating with confinement for days in bed and with pain being amplified by exposure to light, sound, touch or odors. These disabling headaches affect the entire body, causing nausea and sometimes vomiting, diarrhea, constipation, abdominal pain, sore muscles, brain fog, inability to sleep, anxiety, depression, even heart irregularities. In other words, "when your head hurts, the whole body suffers." In describing this variety of symptoms to a clinician, a barrage of different diagnoses often follows.

I think I have been everywhere on the 'spectrum' you just described. Why do doctors make diagnosing headaches so confusing?

Physicians are trained to focus primarily on the symptom of headache and see the primary problem as pain rather than systemic disruption of your nervous system. The various diagnoses you have been given reflect the clinician's best interpretation of symptoms you describe and then the best pharmacological match for the diagnosis they provide. So, the more diagnoses you receive the more treatment and particularly the more medication one is likely to receive.

Confusion occurs around the fact that headache is a nearly universal human experience that creates a spectrum of various symptoms and the potential for many different diagnoses. Worldwide, tension headache is the most common. Migraine occurs in about 12% of humans and cluster affects an estimated 0.5% of the population at least in the US. Of all the primary headaches, migraine is probably the best understood. What we know about migraine is used to explain the other primary headaches, like tension and cluster, so that too can be create even more confusion.

Do I have migraine?

Yes. Migraine is diagnosed when in a person's lifetime at least 5 headaches lasting 4-72 hours occur with the following characteristics: 1) moderate to severe intensity, on one side of the head, and/or throbbing; 2) nausea with/without vomiting or sensitivity to both light and sound.

But that description of migraine is only a small part of the story. The process of migraine may begin hours or sometimes days before the headache. Symptoms may include fatigue, brain fog, sensitivity to light, sound, and odors, irritability, and stiff muscles. These can continue during the headache and even after it resolves. One third of patients sometimes experience another set of warning symptoms called aura. This may develop an hour or so before the headache with flashing, scintillating lights, tingling in the hands, arms, and face, or other symptoms, such as speech problems or dizziness. Sometimes this leads to the false assumption that the individual has a serious eye disease or possibly is having a stroke. When the aura resolves, the headache is usually on its way.

Since you have been having headaches on more than 15 days per month for several years and most of these headaches meet criteria for migraine, your actual diagnosis is chronic migraine. Also, you are requiring medication to treat migraine and other headaches on more than 15 days per month – meaning you have a second diagnosis of medication overuse headache. Through a lifetime, those having frequent, uncontrolled migraine may find themselves burdened with multiple headache diagnoses while living with one of the most disabling diseases in the world--migraine.

Wow, that explains a lot. So, do I have "sinus headaches" too?

Even though you probably have nasal allergies that can be a risk factor or a trigger for migraine, treating allergies and even sinus surgery did not resolve your headaches. It is more likely that during some of your migraine attacks the brain activates nerves in the nasal and sinus structures causing symptoms that often mimic sinus disease. Studies have demonstrated that most people with self-diagnosed "sinus headaches" do in fact have migraine and generally it responds well to migraine treatment.

Okay, I think we're on a roll. Do I have cluster headache?

No. The characteristics of cluster headache include: 1) At least 5 lifetime attacks of a severe or very severe headache lasting 15 minutes to 3 hours that may strike once every other day to 8 times a day; 2) The headache occurs on one side of the head, usually around the eye or in the temple area; 3) On the same side as the headache, there is redness and tearing of the eye, sometimes swelling around the eye or a drooping eyelid with changes in the size of the pupil, nasal congestion and a runny nose; 4) The cluster period may continue for weeks to months and then spontaneously resolves only to return later. Sometimes there is no remission for over a year and then it is called chronic cluster headache.

Unfortunately, those with migraine may be given a cluster diagnosis when a very severe headache is around the eye and accompanied by eye and nasal symptoms. However, based on your history, I do not believe you have cluster headache.

Do I have tension-type headache?

That's a good question. There is a simple answer and a more complicated one. Simply, the diagnosis of tension-type headache is excluded in someone with chronic migraine because non-migraine headaches, such as tension-type headache, are already part of the chronic migraine picture.

The more complicated and perhaps more important answer is that probably you were given a diagnosis of tension headache when your migraine attacks were less frequent and at that point in time it was probably correct by current diagnostic standards. However, one thing most people with migraine realize early on is that not all migraine attacks are created equal and as we discussed they experience a spectrum of attacks ranging from those that are mild to those that are severe. So, within the spectrum of headaches, some are clearly migraine; others that are not quite migraine and labeled by clinicians as probable migraine; and there are another group that are clearly tension-type headache. Differentiating these different expressions of headache is complicated further by factoring in people's efforts to treat headaches. I hope you see diagnosis is not as black and white as many believe it to be.

Often individuals receive many headache diagnoses each with different instructions and medications on how it should be treated. Unfortunately, these treatments may simply delay the use of effective treatment to the point when they are no longer effective. If your headaches are poorly controlled the frequency may increase which then results in increased use of medication. Many individuals get caught in a vicious cycle of frequent headaches and poor response to treatment medications leading to more headaches and more medication. As it is for you, many with chronic migraine are burdened for years by medication overuse headache, severe disability, and misinformation about their diagnoses.

I suggest you think of migraine as being the underlying headache disease that we are working to manage. The origin of migraine is likely genetic, meaning that individuals like you have inherited a nervous system that is more sensitive to their internal and external environments. Changes in these environments can trigger the nervous system to express what seems to be many unique headaches. Another paradox is that a little migraine or one that is just beginning often responds better to treatment than a severe one. Early treatment is more likely to resolve the migraine completely. Late treatment may only take the edge off some symptoms, or it may not be effective at all, resulting in use of many doses of medicine before the headache resolves.

Consider it our job going forward to create a management plan specifically for you. That includes: 1) an understandable diagnosis; 2) having access to the right combination of medications that safely and effectively prevents and treats migraine attacks; 3) education about lifestyle adjustments that will sustain control of this disease for a lifetime.

Well, there is only one question left. Is my migraine caused because I don’t cope well with stress?

Your question exposes a common belief among those with migraine and those that treat patients with migraine: “I am somehow causing my migraines.” No, you are most emphatically not. Migraine is a genetic disease and what you eat, drink, and experience are no different than what people without migraine do in their lives. Your challenge is to organize your life going forward in such a way that migraine is not the centerpiece to how you are going to live your life.

Many individuals with migraine fear when the next episode will occur. This keeps a person on-edge with worry, which, ironically, increases the probability of another migraine. They always have medication available and frequently develop complex strategies for how and when to use each medication they have.

The key to success is to redirect one's attention to an activity that you value and look forward to, such as, swimming, writing, hiking, biking, dancing. Whatever you want to do. When you engage daily in a fun, rewarding activity, you will be less prone to migraine.

Also, identify the areas of your body that signal tension, such as, muscles in the neck or the knot in your stomach. These are warnings that you need to change direction, relax or engage in a fun activity to sooth the tightness before the headache materializes.

It's all a matter of reading and listening to your body and choosing a route of action other than passively living through another migraine. This takes practice. It's not necessarily easy. It won't work all the time but it's a beginning to engage in an activity as an alternative to standing by and waiting for the migraine to occur.

Good luck! You can do it. Perhaps you can receive support from a group of other people living with migraine who are dedicated to erasing the power of migraine from their life.

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“WHAT IS CAUSING MY MIGRAINES?”

JOHN F. ROTHROCK MD

My primary care doctor told me that migraines are vascular headaches. Is there is something wrong with my blood vessels?

For many years migraine was thought to result primarily from abnormal vascular reactivity, with arterial constriction and consequent retinal or brain ischemia producing aura symptoms and "compensatory" dilation of cranial arteries in turn causing the characteristic pulsatile, sickening pain of the disorder. This primary vascular hypothesis gradually has given way to something more complex and, frankly, more interesting. With the ascendance of a "unified" hypothesis that more effectively describes migraines biogenesis, we now think of migraine as a primary *brain* disorder that in some respects is analogous to primary epilepsy.

Although migraine and epilepsy clinically manifest themselves in very different ways, each reflects a brain that is inherently "hypersensitive”. Both in epilepsy and in migraine that hypersensitivity may be reflected on EEG, and in migraine specifically photic stimulation will provoke a disorganized EEG pattern that may include epileptiform discharges. Providing further evidence that individuals with migraine may have hypersensitivity which is especially prominent within the visual/occipital cortex are the findings elicited by visual evoked response (VER) testing: an exaggerated/high amplitude cortical wave that does not “fatigue” with repetitive stimulation. Migraine and epilepsy are bi-directionally "comorbid"; if one has migraine, he/she has an increased likelihood of having epilepsy as well…and vice versa. In the case of so-called "migralepsy", the two disorders blend together clinically such that seizure activity occurs always or nearly always in the setting of an acute migraine episode. If these two clinically distinct disorders similarly reflect inherently sensitized brain cortex, then it should not be surprising that medications which stabilize and desensitize cortex may be effective in treating both (egs, divalproex sodium and topiramate).

Along with the cerebral cortex itself, the various components of migraine’s biologic "circuitry" include the brain stem (and the trigeminal nucleus caudalis of the medulla, in particular), the trigeminal nerve and the synaptic junction that lies between the trigeminal nerve endings and head pain receptors located on the meningeal vasculature. While release of vasoactive peptides at the trigeminovascular junction may produce arterial changes (including vasodilation) that contribute to the head pain of migraine, these changes typically occur as a consequence of a pain signal which arises "upstream" in the circuitry, arriving at the terminus of the migraine circuit via electrochemical transmission.

Two chemicals - protein neurotransmitters - that play major roles in modulating the transmission of head pain signal are serotonin and calcitonin gene-related peptide (CGRP). Medications which activate serotonin receptors that inhibit head pain signaling will "short-circuit the circuit". This appears to be the major mechanism by which the triptans and lasmiditan can terminate migraine episodes. The anti-CGRP monoclonal antibodies (erenumab, galcanezumab, fremanezumab, eptinezumab) and the "gepants" (ubrogepant, rimegepant, atogepant) block the receptor to CGRP or directly inactivate that protein molecule, and in doing so they desensitize the acutely or chronically sensitized migraine circuitry. The fact that these "designer drugs" for acute migraine treatment and migraine prophylaxis were synthesized to "fit" the existing hypothetical model for migraine’s biogenesis and are so clinically effective reinforces the notion that this "unified" model at least approximates what is occurring at the molecular level.

But my headaches are so severe. Surely there is something wrong with my brain. Shouldn’t we do some testing to find out what is causing these attacks of head pain? Maybe an MRI scan?

Even with its astounding resolution and sensitivity, it is beyond the capacity of MRI to visualize the biologic underpinnings of migraine. It appears that primary migraine is likely to be genetic in origin, either inherited or a consequence of gene mutation during embryogenesis. Approximately 50% of migraine patients evaluated in an outpatient setting will report that at least one first-degree family member also has migraine. If first-degree family members of the patient are interviewed directly, that proportion rises to 90% or more. Just under 40 million Americans actively experience migraine, and for them it is no more "wrong" to have migraine then it is to have blue eyes or red hair.

Thus the familiar constellation of symptoms that we term "migraine" appears to result from a genetically sensitized brain and, more specifically, from a genetically sensitized circuit of cortical neurons, nuclei, ganglion cells and axons that, when sufficiently stimulated, activate to produce the symptoms. As a *primary* headache disorder, your migraine is a part of you and your individual biology. Migraine is not a secondary headache disorder intrinsically foreign to you and indicative of an acquired neurologic or systemic disease.

If your history is consistent with migraine, if there are no "red flags" in your history to suggest that either a) something else may be mimicking migraine and causing *migrainous* headaches or b) that you have a new/acquired secondary headache superimposed upon your pre-existing migraine, and if your neurologic exam is normal, then the yield of brain MRI or other neurodiagnostic testing will be extremely low. There currently exists no test - even brain biopsy - that specifically can diagnose or confirm migraine. In rare variants of migraine there are genetic mutations specific for the particular variant, but genetic testing will not assist in the diagnosis of more typical migraine. To date, investigators have identified over 40 genetic mutations associated with the most common clinical types of migraine…and there may be many more. We have a long way to go before genetic testing will be helpful in diagnosing and managing migraine.

But my migraine is much worse than my twin sister's. And my mother's. Why should that be?

While your genetic predisposition to migraine may be similar or identical to that which produces the migraine experienced by your sister and mother, many factors intervene to influence how much or little that genetic predisposition will be clinically expressed. The process by which these influences promote or inhibit gene expression is termed *epigenetics*, and it's likely that although our genome itself is fixed, our *epigenome* is constantly changing as we pass through life.

The migraine circuitry is highly responsive to changes in the internal and external environments. For example, in women migraine may worsen clinically as a consequence of the natural fluctuation in the sex hormone levels that they experience during a menstrual cycle, as a consequence of pregnancy, or in the perimenopausal years. For both genders, changes in barometric pressure, sleep habits or dietary routine may influence one's migraine burden, and physical or emotional stress is a commonly cited aggravator of migraine. The migraine you experience as an adult may even reflect epigenetic changes that occurred much earlier in life; for example, the emotional nurturing you receive during early childhood appears to influence both the age at which you first begin to experience migraine and the likelihood of your eventually developing the chronic variant of migraine. There is even evidence that the epigenome may be inherited along with the genome itself. In other words, the way you feel and behave in this moment may in part reflect circumstances that affected your forebearers in the generations preceding you.

Again, no "triggers" or "aggravators", internal or external, represent the cause of your migraine. Instead, they are potentially modifiable external factors that act upon your intrinsic biogenetic predisposition to experiencing migraine. Stress may aggravate migraine, but it is not the cause of your migraine. Your migraine may routinely activate the day prior to menstrual flow onset, but this implies neither that your hormones are abnormal nor that hormonal fluctuations are the primary cause of your migraine.

Can my migraine be cured?

As evidenced by descriptions written in Mesopotamia thousands of years ago, migraine has co-existed with humankind for an awfully long time. For whatever reason, natural selection - the pruning shears of evolution - has not seen fit to eliminate migraine from our midst, and the disorder remains highly prevalent in our general population. It is, if you will, a "part of us", and to speak of "curing" migraine is much the same as seeking to "cure", say, a propensity for motion sickness.

The day may come when we can perform gene editing, identify the particular genetic permutation that is producing a given patient's migraine, intervene to "engineer" that permutation so as to silence its clinical effect and thus "cure" migraine. Until then, however, the best we can do is attempt to modify migraine’s natural course in a positive manner by prescribing pharmacologic and non-pharmacologic therapies that serve to desensitize migraine’s biological circuitry. Even when therapeutic intervention is wildly successful and the patient becomes headache-free or nearly so, migraine is still there, lurking beneath the surface, biologically present even if clinically quiescent, and the patient remains at risk for eventually experiencing recurrence of migraine episodes.

Why have I not responded to so many of the migraine therapies I have been prescribed?

First, did your lack of response to a medication prescribed for migraine prevention result from your failure to administer an adequate dose of that medication for an adequate amount of time? Did your lack of response to a medication prescribed for acute migraine treatment result from your administering that medication at a point in the migraine episode where it was predestined to fail?

Even when a migraine therapy is administered optimally, there is no guarantee of success. Again, there appear to exist many genetic permutations associated with migraine, and it's reasonable to presume that at the molecular level there may be variations in the structure and physiology of the migraine circuitry previously described. For example, in some migraineurs serotonin may assume a relatively minor role relative to CGRP, or vice versa. In others, neither neuropeptide may dominate, nor will glutamate, an excitatory neurotransmitter, serve as the driving force behind generating and conducting the head pain signal.

If this presumption is correct, then one should not expect any given therapeutic intervention to be 100% effective in <u>all</u> migraineurs, and arriving at an effective treatment strategy is typically is a matter of educated trial and error. There is a real scarcity of variables which will assist healthcare providers in predicting which migraine patient will respond to a given migraine therapy.

To make things even more complex, it's logical to assume that the molecular components of migraine's biologic circuitry are dynamic, with receptor sensitivity changing either as a consequence of migraine attack frequency, alterations induced by prophylactic therapy, epigenetic influences or simply the advance of years. To treat migraine effectively, then, one must be nimble and prepared to shift an existing treatment strategy so as to match the concurrent migraine burden.

Despite its prevalence, migraine is a complex disorder that poses a challenge to those who attempt to treat it. That's the bad news. The good news: over the course of the last three decades we have been witness to nothing less than a revolution in our understanding of "what causes migraine". With this understanding has come a veritable deluge of new therapies offering the migraineur new options for management that are safe, well-tolerated and clinically effective.

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WHAT KINDS OF THINGS CAN TRIGGER MY HEADACHES?

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It's frustrating but I kept a log, and I can't seem to find any specific thing that triggers my headaches. Is that common?

You are certainly not alone. Many patients are frustrated by the inability to identify the "cause" of their migraines. They may believe that by avoiding their triggers or making easy changes in diet they may rid themselves of their headaches. Unfortunately, things are not so simple. Although I find that most patients can identify at least a few triggers for migraines, this is not true for everyone. Some have no triggers. Migraines can often occur randomly, without any obvious triggering mechanism. Others report that many of the things they believe would bring on a migraine "don't do it every time." The brain of a migraine person can be influenced by multiple internal factors and therefore react unpredictably to various external factors. Some people also require the accumulation of several triggers which only cause migraine when seen in combination. For example, certain women report red wine as a trigger for migraine, but only when consumed during the time of a menstrual period. Finally, more than a few migraine patients are just unfamiliar with possible triggers and simply don't know what to look for when completing their diaries. Don't get discouraged. We can review a list of the most common migraine triggers and I'll encourage you to continue keeping a headache diary for another three months.

What are the most common triggers for migraines?

The migraine brain is very sensitive to *change*. Stress is widely accepted as the most common migraine trigger, but it is the *change* in stress levels that most commonly is connected to the start of a migraine or series of migraines. An abrupt increase in stress – for example an argument with your boss - can bring on attack, but so can relaxation after a period of stress. Some get the headache the week of final exams or a funeral, while others