

Kayley

My name is Kayley, I've been getting migraines since I was a kid. But over the last eight years or so, it's become a battle against chronic daily migraines. The singular worst pain I've ever felt in my life, I will never forget it. It was January 2019 at 3 a.m. during a blizzard. I woke up with a 10/10 pain scale migraine, which is the kind where you worry that maybe this time it's actually something more serious like a stroke or meningitis. It takes a lot to get me out of my bed to drive myself to the hospital during a snowstorm to get an IV shoved in my arm. Hopefully that gives some indication of how miserable these things are. They are not just headaches, for every day that I have actual migraine pain, there's a period afterwards of what I call the migraine hangover where you're just completely drained and foggy and the nausea can be horrific. And I get really sensitive to smells both as a trigger and in terms of getting phantom smells before a migraine hits, which is bizarre. It could be a totally debilitating thing and it could be really hard to feel like you're being taken seriously because it's invisible. It's incredibly frustrating to have to cancel plans or call off work because you have another migraine. But sometimes over the counters or even your prescription migraine medicine just still isn't enough to make you functional enough to go about your day.

Katy

I'm Katy and I have chronic migraine. Chronic is defined as 15 or more days a month with migraine symptoms. I average about 28 days a month. I've had migraine pretty much my entire life. My mom also has migraine, so when I was five or six years old and started getting excruciating headaches so bad I threw up, my parents knew what was going on. At the time there weren't a lot of migraine drugs available and especially not for young kids. So it was just over the counter painkillers, a caffeinated drink, and a nap. Over the years I also started having abdominal migraine, like regular migraine but the pain was mostly in my stomach. In high school I occasionally had vestibular migraine where the primary symptom is intense nausea and dizziness without much head pain and which could last for months at a time. I carried on having a few migraine episodes a month through college when I got sumatriptan, an older abortive drug which worked for a while. Still about once a year, nothing would work and I'd have to go to the ER for an IV cocktail. Then in my mid 20s the medication stopped working as well, the episodes became a lot more frequent until they were chronic, and they've been that way for about three years. In that time I've tried most treatment options, some of which didn't work at all and some of which had side effects I couldn't tolerate. Right now I've landed on one anti epileptic drug that helps. I get an IV infusion of monoclonal antibodies once every three months and I take a pill nightly and then another pill when I'm getting a migraine. Even though they don't completely treat my migraine, these drugs are huge for my quality of life but they're also really expensive. So I spend a lot of time on the phone with insurance. I also use a neurostimulation device in my trigeminal nerve to try to prevent and manage migraine, I have a hat made of ice packs to help with head pain, I see a therapist who specializes in chronic illness, I stay extremely well hydrated, I never leave home without sunglasses, and I try to be realistic when I'm feeling especially bad and take it easy which is sometimes easier said than done.

Anonymous

The first sign that a migraine is brewing is that my eyes start misbehaving. I get my migraines solely on the right side of my head and things just look brighter out of that eye. It feels like that eye is open wider than the other even though it isn't. I'll have flashing lights and sometimes it's hard to find words. Sometimes I can avoid getting a full on migraine if at that particular instant I take a CGRP inhibitor rescue medication, eat a candy bar and drink a diet soda. If not, the pain starts in the top back part of my head. There was a migraine commercial a long time ago that showed lightning bolts radiating out of a spot on the woman's head and that's what it feels like. Light, sounds, smells, and heat become painful. My cheek feels like something is pressing inward. Sometimes if it's bad enough, my jaw and teeth start hurting and the pain begins to radiate down my back. At this point, pretty much all is lost and I have to go lie down. Strangely, it helps to lie down on my right side and press the painful part into the pillow. It may be the cool pillow or the pressure. But if I can get to sleep, I'll generally be better the next day.

Darcie

My name is Darcie, I'm 28, and I started having migraines when I was around 10 years old. I've been diagnosed with chronic migraines but I also have atypical migraines occasionally. So when I was 19, I woke up one morning and the right side of my face and my right arm felt a little tingly. The more I moved around, the worse the tingling got, to the point where the right side of my body was just starting to feel numb. We let a couple of hours pass I think and nothing was changing. So at this point my parents were starting to feel pretty concerned because when you think about someone with symptoms of having one side of their body be numb, you think about someone having a stroke. So we go to the hospital and one thing I'll never forget about this day is when we got there, they needed me to sign some sort of paperwork and I couldn't do it. My hand was so numb that I couldn't hold a pen properly. They did all of the tests that you would do for a stroke, all of which came back completely normal. After the test a doctor came in and he asked me do you have migraines? And I said yes. And he said I think what you're experiencing is an atypical migraine, which I had never heard of before. But he explained to me that they can come in all different shapes and sizes but some of the more common types present as stroke symptoms. It took about two weeks for the numbness to completely fade away. But even now, almost 10 years later, I still have a small spot above my right eye that just doesn't feel quite right. But that's my atypical migraine story. Definitely one of the scarier days of my life but I am grateful because I know what it feels like in case it happens again.

Kathryn

Hi, my name is Kathryn, I'm 35 years old, and I've been having migraines since I was about 12. These progressed to having about 15 to 20 headache days per month. I had a lot of anxiety around my triggers such as flying in airplanes, weather changes, too much sun or heat, certain foods, and fluorescent lighting. I'm a veterinarian so I went through a lot of schooling and school could sometimes be difficult since the migraines cause me a lot of pain and to lose concentration. I was taking over the counter pain medications almost every day and I worried about long term damage to my organs. I tried everything from diagnostics such as MRI, supplements, preventative medications, and glasses that would reduce the blue light from the fluorescent lighting. And thankfully this all changed about two years ago when my neurologist prescribed the new monoclonal antibodies, the CGRP inhibitors. I have the monthly injection for prevention and an oral abortive and this has absolutely improved the quality of my life and reduced the severity and frequency of my migraines.

Chris

Hi, my name is Chris, I'm a 26 year old transgender man, and I've been dealing with migraines for most of my life. It all really started rolling when I was in middle school, so around 12 years old, and I started having weekly if not multiple times a week bouts of what I thought at the time was food poisoning. My head would hurt like there was someone blowing up a balloon inside it and there was just no space for anything to go. And the light would hurt my eyes. I would get incredibly dizzy and nauseous and I would have to excuse myself, go to the bathroom, throw up, and return to class because that was really the only option I had. This kind of just continued for years and years. I never really had a chance to get things checked out until, god, now 14 years later. Now that I am an adult working in the healthcare system, I have decent insurance. So over the past 12 months I have had two MRIs that showed absolutely nothing out of the ordinary. It's hard to stay hopeful in terms of treatment and possibilities, especially considering that we have no idea where this comes from. I almost was hoping that we would discover a freak brain tumor or something like that because that would mean a real answer. It's always an interesting concept to grapple with knowing that this is something that is so incredibly common and we just have so few answers as to why so many people deal with this. But it is something that I know there is a lot of research happening with. And despite having a very rocky history, I do remain hopeful overall.

TPWKY

(This Podcast Will Kill You intro theme)

Erin Welsh

Thank you everyone who shared your story with us. We really appreciate it. We really do.

Erin Allmann Updyke

Yeah. Thank you for taking the time to write to us and to share your story with us and with everyone. Yeah, thank you.

Erin Welsh

Hi, I'm Erin Welsh.

Erin Allmann Updyke

And I'm Erin Allmann Updyke.

Erin Welsh

And this is This Podcast Will Kill You.

Erin Allmann Updyke

And today we're talking migraine.

Erin Welsh

Yeah. What a topic, Erin.

Erin Allmann Updyke

What a topic.

Erin Welsh

I feel like I recently said something about oh, this is the most requested topic. And I was wrong because it's got to be migraine, right?

Erin Allmann Updyke

I think it's definitely, it's up there.

Erin Welsh

It's up there. Yeah. And so I really sort of feel like this has been A) a long time coming, but B) I still feel weirdly unprepared despite how much reading I know that we've both done on this.

Erin Allmann Updyke

Same. I always feel unprepared.

Erin Welsh

Yeah.

Erin Allmann Updyke

And then when it comes to brain stuff, I feel like an extra layer of unprepared. But today it's still going to be a great episode, promise.

Erin Welsh

Oh yeah, for sure. And I feel like listeners of the podcast have gotten used to sitting with the unknowability of certain things.

Erin Allmann Updyke

Yeah.

Erin Welsh

Aka, great question, I don't know.

Erin Allmann Updyke

I think that's one of my favorite parts about our podcast.

Erin Welsh

Me too. Me too. Another favorite part of our podcast is guess what?

Erin Allmann Updyke

Quarantini time, that's what.

Erin Welsh

It absolutely is.

Erin Allmann Updyke

So what are we drinking this week?

Erin Welsh

This week we're drinking The Hammerhead because migraines are debilitatingly painful.

Erin Allmann Updyke Yeah.

Erin Welsh And it feels like a hammer.

Erin Allmann Updyke In your head.

Erin Welsh In your head.

Erin Allmann Updyke Ow.

Erin Welsh Yep.

Erin Allmann Updyke What's in The Hammerhead?

Erin Welsh In The Hammerhead is essentially like a boozy affogato.

Erin Allmann Updyke Yum.

Erin Welsh So good. It's got espresso which you can do decaffeinated if you would like, it's got ice cream naturally, it's got bourbon, and it's got a little bit of amaretto.

Erin Allmann Updyke Yum. We'll post the full recipe for that quarantine as well as our non alcoholic placeborita on our website thispodcastwillkillyou.com and on our social media channels, of course.

Erin Welsh Of course. On our website thispodcastwillkillyou.com, you can find all sorts of cool things. We've got transcripts, we've got links to merch, to our bookshop.org affiliate account, to our Goodreads list, to music by Bloodmobile, to our Patreon. You can find the sources for each and every one of our episodes. There's probably more stuff. How do we not have this down by now?

Erin Allmann Updyke Oh I thought you did a phenomenal job.

Erin Welsh Thank you, thank you. I try.

Erin Allmann Updyke Well with that, shall we get into the biology of migraine?

Erin Welsh Yes please.

Erin Allmann Updyke All right. We'll take a quick break and get to it.

TPWKY (transition theme)

Erin Allmann Updyke So what even is a migraine?

Erin Welsh That sounds like a great place to start.

Erin Allmann Updyke

That's where we're gonna start. I'm going to start with a quoted definition which happens to be from a pretty old paper but the definition holds. So we'll start there. This is from a New England Journal of Medicine article from 2002, which says quote: "Migraine is a common chronic incapacitating neurovascular disorder characterized by attacks of severe headache, autonomic nervous system dysfunction, and in some patients, an aura involving neurologic symptoms." Unquote. Biology section over. That's our definition. So that's the jargon version. The way that I'm going to break down this biology section is to try and give you an idea of what migraine really is and as much as we can know about what's happening during these migraine attacks.

So a migraine attack can be divided into 3 to 4 main parts or kind of like sections and then there's inter migraine intervals, like between migraines. So first we'll go over what these parts or what these phases of a migraine attack are, what they look like, what they feel like, which you heard a lot of in our firsthand accounts. And then we'll go over what we know so far about what's happening in our brains during these attacks. But forewarning, as will come as a surprise to no one listening to this episode if you've ever listened to TPWKY before, there's a lot that we don't know. But there is some stuff that we do know and so I'll try to get into some of the nitty gritty of that as well.

So a migraine attack generally starts with a period of prodromal symptoms. This period is often called the premonitory symptoms period, which can start anywhere from two hours to two days prior to the actual headache that most of us associate with migraine. So these symptoms can range from anything like fatigue or yawning or impaired concentration, you could have neck pain or stiffness, water retention, nausea, photophobia, which is difficulty looking at light, you might have food cravings. It's a really long and kind of diverse list of symptoms that someone could have for up to two days, right, a day or two before the migraine attack itself. About 80% of people that get migraines have some kind of these prodromal symptoms.

And then for about 30% of people with migraines, the next phase is an aura. And a lot of people have probably heard of an aura. But a, n aura are these very bizarre transient focal neurologic symptoms of various kinds, most often like 90% of the time, it's these visual symptoms. The most common one is called a scotoma or a scintillating scotoma, which sounds fancy but in fact is terrifying, having had these episodes. It starts as a flickering spot, a flickering kind of light spot either in one eye or in both eyes. And then this spot can kind of grow or move or change and keep flickering. And scotoma just means like a blind spot. So wherever you see this flickering wave or curve of light, you can't really see anything except that light, but the vision around it usually remains the same. And this might expand or people can see different kinds of patterns like a crescent or a zigzag or different shapes and then eventually it just stops.

But an aura isn't only visual, that's one type of aura. People can also have paresthesia, so like feeling tingling or prickling sensations, usually just in one part of the body or it could be like a numbness of the face or your arm. It could even be things like difficulties with expressive language, not being able to find your words or not being able to say words the way that you could just minutes prior. And even more rarely, an aura could be some kind of motor dysfunction, like all of a sudden not being able to use your hands or your legs. A lot of this might sound a lot like a stroke because some of these symptoms can really mimic that. So this aura phase usually starts anywhere from five minutes to an hour prior to the onset of the headache. And it usually lasts under an hour and is followed pretty immediately by the headache part of migraine. That's the part that people think of when they think of migraine most often. So let's get to that.

What is a migraine headache itself? Aka how do we define a migraine headache vs any other kind of headache? So first this is a headache that most often is unilateral, it's on one side of the head or it at least starts off on one side of the head and then it might move to the rest of the head. It's usually described or characterized like a throbbing pain or like a pounding pain rather than a tension type pain. And in general, a migraine is classified as moderate to severe intensity. Like the pain is bad enough that you can't get out of bed, you feel like you need to just lay down. And that's also in part because the pain generally increases with activity which essentially forces you to just lie down. So those four characteristics, unilateral, throbbing pain, moderate to severe intensity, and increasing with activity, based on the international classification of headache disorders, which is the criteria that are used to diagnose migraine, a migraine has at least two of those four criteria.

Erin Welsh

Okay.

Erin Allmann Updyke

And on top of that, migraine has either nausea and vomiting and/or photophobia or phonophobia, so severe light or sound sensitivity. I know, your face.

Erin Welsh

It sounds like... I know many people that have migraines. My mom, my grandma had horrible migraines her whole life. And I think it's just when you lay out all of the things that you can experience, it's just horrific.

Erin Allmann Updyke

It really is. And here's an even more horrific part, the duration.

Erin Welsh

Yeah.

Erin Allmann Updyke

By definition, a migraine is also a headache that's lasting between 4 and 72 hours. I'm going to say that again. This is a severe headache with nausea or photophobia, not being able to look at light, that increases with activity, that's throbbing in your brain for 4 hours at a minimum or 2 hours if you're a kid, and it can last up to three days, meaning you go to bed with a headache and you wake up with this same headache. And a migraine isn't even over when it's over because the fourth phase of migraine is the postdromal phase. And this can last again another 1-2 days after the headache subsides. This recovery phase can have increase in tiredness or somnolence, it can have difficulties in concentration. A migraine altogether is a phenomenon that affects the brain on a pretty large scale. And the full duration of a migraine attack can last up to seven days if you include the premonitory and the recovery symptoms as well as the headache itself.

Erin Welsh

I've heard it described as a symphony in four movements but I feel like that's way, way too pleasant language to describe what's happening.

Erin Allmann Updyke

I agree. That sounds like a symphony is like nice. This is a cacophony in four movements.

Erin Welsh

Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

Oh my gosh.

Erin Allmann Updyke

I know. And that's just how we define the migraine. So of course then knowing all of this, knowing how debilitating a migraine can be, how severe it can be, the question or questions are like why does this happen? How does this happen? Who does this happen to? How can we stop this and never have this again? As promised, I do not have all those answers.

Erin Welsh

But you have some of them.

Erin Allmann Updyke

I sure do. So here is what we do know or at least what the consensus so far is about what we think is going on in the brain with a migraine. So what we know so far is that a migraine headache depends on the activation of a pathway in our brain called the trigeminovascular pain pathway. And it very likely involves a little peptide called CGRP or calcitonin gene-related peptide. This is a neuropeptide, we'll talk about it in a little bit more detail. But let's define some of these things, shall we?

Erin Welsh

Yeah.

Erin Allmann Updyke

So the trigeminal nerve you may have heard of, this is cranial nerve number five. So this is one of our 12 cranial nerves that is responsible for all of the sensation to our face pretty much and also innervates muscles that are involved in chewing and biting. So this is a predominantly sensory nerve, it's mostly carrying information from the face to the brain and then from part of our brain stem into the cortex of our brain. And then there are some nerves that are also involved with muscles and so are more efferent, sending signals for muscle contraction, right. So this trigeminal nerve, mostly sensory and like many nerves, most nerves, is very interrelated with vasculature. It forms complexes of nerves and arteries and veins. And in the case of the trigeminal nerve, it's projections especially in our brain are very strongly associated with the vasculature in our brain and our meninges, that's the covering of our brain and spinal cord, both the dura mater, which is the outer layer of our meninges, and the pia mater, which is the innermost layer of our meninges.

So this trigeminal complex as it's called has these ascending nerve axons that project into a whole bunch of brain regions, in our brain stem, our hypothalamus, our thalamus, our cortex. All of these regions of our brain are involved in a whole bunch of stuff that we happen to see dysregulated during a migraine. These involve our response to pain and nociception. So nociception is just the actual nerve signals of pain, like our nervous system getting those signals is the process called nociception, our nociceptors are pain nerve fibers. There are a bunch of other neurons that are projecting to parts of our auditory visual and olfactory system, parts of our cortical brain like regions that are involved with movement or even concentration, all of these different brain regions that happen to correspond to a lot of the non pain symptoms of migraine as well as these nociceptive or pain-related symptoms. So think things like photophobia, nausea, vomiting, difficulty focusing, all of that. So we know that the trigeminovascular complex is activated and involved in this process of migraine and in kind of all of the phases of it.

Erin Welsh

But why?

Erin Allmann Updyke

Erin, have I ever answered a why question on this podcast actually?

Erin Welsh

I'm sure that you have, yes.

Erin Allmann Updyke

I'm not going to right now.

Erin Welsh

No.

Erin Allmann Updyke

That's where we'll get to the part where I go I don't know.

Erin Welsh

Okay.

Erin Allmann Updyke

But let me tell you more about what we do know.

Erin Welsh

All right, all right.

Erin Allmann Updyke

So we know that it's the trigeminovascular complex that's activated. We also know that this specific peptide, CGRP, calcitonin gene-related peptide, is very involved in this process. This is a peptide that we see released by this trigeminovascular complex during migraines. And we now know that blockade of this peptide or its receptors by various medications is effective in many cases at stopping migraine. We think that CGRP acts predominantly in the dura mater, so the outer layer of our meninges, and that what it does is modulate the trafficking of these nociceptive signals. What does that mean? It means that CGRP is involved in the sending and receiving of the pain signals that are involved in migraine. And it may also be involved in inflammation. And there's still some thought that inflammation is involved in the migraine process.

Erin Welsh

So if you're blocking that or stopping that neuropeptide through whatever medication, then it's like okay, it can't be the messenger that causes all the pain and that also then leads to inflammation.

Erin Allmann Updyke

Exactly.

Erin Welsh

And so in terms, maybe this is jumping ahead a little bit, but in terms of when you say stop a migraine, at what point can you stop a migraine? Is there like a threshold beyond which, like the point of no return I guess?

Erin Allmann Updyke

That's a really good question. In general, all the medicines that we use for migraine, especially for like acute migraine attacks, work best the earlier that they're given. And part of that is because once this process starts rolling and especially once the pain has really started to take hold, there's an additional process we think of central sensitization. So there's a thought that once the pain signals have started to be sent, now our brain is acting a little bit on overdrive in response to those signals. And then yeah, you're right, that's a really hard ball to stop rolling essentially.

Erin Welsh

Okay. So it's like ah, that old pathway.

Erin Allmann Updyke

Exactly.

Erin Welsh

I know it well. And then you just speed down it and then pain goes up.

Erin Allmann Updyke

Yeah.

Erin Welsh

And the variation in how long a migraine can last. So like let's say that you don't stop the neuropeptide in time or you lived in a period before there were drugs that could do that or you don't have access to drugs, whatever. Is the variability in how long that migraine will last is just sort of like the half life of the neuropeptide in your brain?

Erin Allmann Updyke

I mean maybe, no, yes. Who knows?

Erin Welsh

Okay, okay.

Erin Allmann Updyke

The answer is that we have no idea because everything that I just told you is a lot of information. It's a level of understanding that we did not have say 15, 20 years ago.

Erin Welsh

No.

Erin Allmann Updyke

But it's also not helpful at all when it comes to understanding the why or even how this trigeminovascular system is activated in people with migraine to begin with. We don't understand the initiation of migraine pain, we don't understand why it stops eventually, why it lasts for as long as it does, why it can be so different both between individuals as well as in one individual throughout their lifetime. There is so much that we don't know.

Erin Welsh

It's really frustrating.

Erin Allmann Updyke

It is. It is. And then there's aura.

Erin Welsh

Oh gosh.

Erin Allmann Updyke

Aura is very interesting. It happens in about 30% of people with migraine, so it's not the most common form of migraine, migraine with aura. And it can happen in absence of a migraine headache as well but that's even more rare. And here again we know a little bit about the mechanisms but so much remains unknown. Aura is thought to happen from a phenomenon called spreading depolarization or cortical spreading depression. Depression, depolarization, same thing. And so when we have an aura, the symptoms tend to start kind of small and they grow or kind of propagate rather slowly, especially compared to another rapid depolarization phenomenon that we've talked about on this podcast, a seizure.

Erin Welsh

Okay.

Erin Allmann Updyke

And so it's thought that what's happening during this time is that starting from some focal point in the brain, there's this membrane depolarization, and that's what happens whenever a nerve is firing, like a signal is firing. But this is happening all in this one area and then propagating along the cortex of the brain.

Erin Welsh

Like dominoes.

Erin Allmann Updyke

Kind of, yeah. And we have like MRI and PET scan studies that show additionally changes in blood flow, like hyperperfusion followed by hypoperfusion, so like more blood flow and then all of a sudden less blood flow, in regions of the brain that are corresponding to the symptoms of aura. And there's evidence that this cortical spreading depression, this depolarization, can then trigger or activate the trigeminovascular system. But we still don't know what the susceptibility is for this cortical spreading, depolarization or depression, and we also don't know why is it then that only 30% of people have aura with their migraine, etc. Like there's some oh this is involved and it activates the system and maybe that's the pathway to the migraine pain. But what about when you don't have an aura? Because people with migraine with aura can also still have migraines without aura. So it's complicated.

Erin Welsh

So I wrote down a few questions.

Erin Allmann Updyke

Okay.

Erin Welsh

Because I knew that I was going to forget them and I feel so overwhelmed by questions, I'm like brimming right now, overflowing.

Erin Allmann Updyke

Okay, okay, okay. I'll try.

Erin Welsh

Okay. Why is the pain typically on one half of your head?

Erin Allmann Updyke

Great question. So our cranial nerves are all paired, which means that you have two sets of them and then you have two sets of those ganglia or the nerve bodies, and then two sets of those like ascending axons as well. So probably you're having activation of one of your trigeminovascular complexes like on one half of your brain at a time.

Erin Welsh

Okay.

Erin Allmann Updyke

That's my best guess. Why Erin? I just told you, I don't know.

Erin Welsh

Okay, okay, okay. I'll try to stay away from the why's. Okay, another question I had was about the mechanism of aura as far as we understand. So you discussed how visual aura is the most common, are the mechanisms the same for the other types of aura?

Erin Allmann Updyke

Great question. Yes, it's thought that in general the mechanism of aura is this cortical spreading depression and what your symptoms are will depend on where that depolarization is happening in your brain.

Erin Welsh

And we don't know how aura is or is not linked to migraine pain mechanistically.

Erin Allmann Updyke

We know from animal studies that the process of this cortical spreading depolarization can lead to activation of that trigeminovascular complex. How exactly we don't know but we do see that correlation there.

Erin Welsh

Okay, one last question.

Erin Allmann Updyke

Okay.

Erin Welsh

So you mentioned earlier when you were describing the various symptoms that can be associated during the migraine pain, like the headache part of migraine, and you commented on how similar they are to stroke. Why? How? Sorry I said why. How?

Erin Allmann Updyke

I don't have a lot of how's for you either, Erin. So that is kind of a can of worms question. And in part it's because it does get into associations that exist between migraine and other neurologic and psychiatric disorders including stroke. I don't have an easy, good answer for like why can migraine symptoms, especially aura symptoms, mimic a stroke. But they can. They also can mimic some forms of seizures or epilepsy.

Erin Welsh

Yeah.

Erin Allmann Updyke

So I want to go into a little bit more detail, not necessarily on this pathophysiology but on the big picture of migraine and migraine biology. Everything that I went over and the criteria that are in the ICHD-3, those are all for migraine, called classic migraine, and migraine with aura. There is also a distinction between what's called episodic migraine and so-called chronic migraine. But the term chronic migraine is confusing and a crappy term because most people who have migraines have them chronically. But what chronic migraine actually means is that people have a very high frequency of migraines. Chronic migraine is classified as at least 15 headache days per month.

Erin Welsh

Oh my god.

Erin Allmann Updyke

Yeah, that's half of a month. And at least eight of these headaches meet criteria for migraine. Some of them can be non-migrainous headaches. Up to 5% of people with migraine meet criteria for chronic migraine at some point in their migraine lifespan because migraines can also change over time. But there are other types of migraine as well that I'm not going to really get into detail on but I just want to mention that they exist because they're important. There's abdominal migraine, which is much more common in kids but can persist into adulthood. It's very similar in terms of all of the prodromal symptoms but instead of headache pain, it's intense abdominal pain that lasts between 2 and 72 hours. And it has very similar non-pain symptoms, nausea, vomiting, photophobia, all of this. Yeah. I have a great paper if you want to read more details about it. But there's a huge connection between the mind and the gut and there's associations between migraine headache and abdominal migraine. There's a lot there.

Migraine is also in relatively large part genetic, about 40%-60% of expression of migraine is from genetic factors. But that being said this is nowhere close to a one-gene, one-disease problem. There are 38 different loci so far that have been identified as increasing our susceptibility to migraines. But there are also a handful of monogenic migraine syndromes. These are a single-gene mutation that also leads to migraine. And these, while they're quite rare, have become really important in terms of studying and understanding migraine because we can identify the specific changes that happened as a result of this one genetic mutation. One of those that I just want to shout out is called familial hemiplegic migraine and this is characterized by migraines, they're hereditary. And in addition to having all the features I just talked about of migraine and aura, they also cause a temporary hemiparesis, which means a one-sided muscle weakness, really looks like a stroke.

Erin Welsh

Yeah.

Erin Allmann Updyke

And there are four different subtypes of this particular monogenic migraine syndrome and they're caused by missense mutation in genes that are involved in neurotransmitter function, specifically in these voltage-gated ion channels. And I know that that's a lot of biochem words but the point is that it's these specific ion channels that are responsible for passing information in our brain that are involved at least at this level of migraine. So it gives us a lot of idea on potential targets for migraine treatment, both for people with these gene disorders as well as migraines in general.

Erin Welsh

That's really interesting.

Erin Allmann Updyke

Yeah. So there's a lot of work on like mice model studies and things like that with these types of migraine disorders. But I'm not done.

Erin Welsh

Okay. Can I ask a question before we go on?

Erin Allmann Updyke

Yeah.

Erin Welsh

Okay. So it was when you mentioned abdominal migraines.

Erin Allmann Updyke

Yeah.

Erin Welsh

And I remembered I wanted to ask about like why the nausea and vomiting and how, at least I read in some historical accounts, people felt better after vomiting and then everything was fine? Which like I'm sure is not a universal truth. But is it just that like there are pathways that are connected?

Erin Allmann Updyke

So yes. In part it's because these trigeminovascular complex afferent nerves, the ones that are going from parts of our brain to other parts of our brain and carrying signals with them, are going to parts of our brain that might be involved with causing nausea, like involved with maybe our vestibular system or something. But it's also because the spinal trigeminal nucleus in our brain stem, in addition to receiving information from our trigeminal nerve, it also gets information from a bunch of other nerves like our facial nerve, our glossopharyngeal nerve, and our vagus nerve, which is our main parasympathetic nerve. And so whenever you have a mess up in our parasympathetic system, you can have a lot of very generalized symptoms.

Erin Welsh

Right.

Erin Allmann Updyke

Now why would people feel better after they barf? I don't know.

Erin Welsh

Okay.

Erin Allmann Updyke

But yeah, it's all complicated, it's all involved. But if all of that wasn't enough, as I kind of briefly mentioned when you brought up stroke, Erin, there are also associations that are not well understood mechanistically but definitely seem to exist epidemiologically between migraine and a bunch of neurologic and psychiatric disorders. This includes epilepsy, it includes stroke, depression, anxiety, and probably more than I'm not mentioning. And one of the things that kept coming up in everything that I read that was so interesting about these relationships is that they're often described as bidirectional. For example, having an episode of major depressive disorder puts one at higher risk of having migraine and having migraine puts one at higher risk of having major depressive disorder, at least based on some epidemiological studies, like in both directions.

Erin Welsh

That sounds like a horribly vicious cycle.

Erin Allmann Updyke

Exactly.

Erin Welsh

How do you break out of that? Can you?

Erin Allmann Updyke

Right. And the same is true for epilepsy. Migraine and epilepsy are these comorbid conditions that seem to similarly have this bidirectional relationship which maybe suggest some underlying similarity in the pathophysiology but we don't know. And it's also associated with an increased risk of stroke, especially in the case of migraine with aura and specifically in the highest risk in people assigned female at birth under age 50. And then there's triggers.

Erin Welsh

Yeah.

Erin Allmann Updyke

When it comes to migraine triggers, there's not really one thing that is true for all individuals with migraine. And we don't know. Because we know so little about the mechanisms of migraine initiation, we don't know how triggers that people may have identified in themselves trigger a migraine in them or in anyone else. But there are some things that seem to be relatively common triggers for most people that experience migraines. And these are things like stress, which could be emotional or physical stress, lack of sleep or poor sleep quality, including jet lag, and hormonal fluctuations, in particular estrogen or a withdrawal of estrogen compared to where you were at previously. This is often a huge precipitant or trigger, especially for people who menstruate. We have very significant hormone fluctuations on a cyclic basis, so for some people that means increases in migraines with periods, for some people pregnancy and breastfeeding causes a decrease in migraine symptoms, and then menopause causes an increase in migraines. Whereas postmenopause might be a decrease or an elimination entirely of migraines.

Erin Welsh

It's like it's just not complicated at all.

Erin Allmann Updyke

No.

Erin Welsh

It is so straightforward.

Erin Allmann Updyke

Yeah.

Erin Welsh

And I'm sure consistent for every person.

Erin Allmann Updyke

I know. Yeah, totally. You can predict it, right?

Erin Welsh

Yeah, totally. And how are hormones thought to be related? Dunno. Okay.

Erin Allmann Updyke

Oh Erin, not a clue. I mean we think that it's estrogen. What is estrogen doing or what is the withdrawal of estrogen doing, like the sudden decrease in estrogen? I don't know, no idea. And it's not like it's universal, right? Not only that not everyone who menstruates has a migraine but even people who do menstruate who get migraines may or may not have any association with their menses. So it's not even close to universal.

Erin Welsh

We have no idea what's happening.

Erin Allmann Updyke

Yeah. I mean and yet we know so much more. Like it used to be thought that it was all about vasodilation and it was all vascular and it's not. So we know a lot more than we did. And you're right, we still know so little. The good news is that what we do know has led to the creation of a lot more effective medicines for treatment of migraines. So despite the fact that there's a lot that we don't know, there is good news to be had and that is that migraines for many people are treatable. There's a number of different medicines, some of them like the triptans work at the 5-HT or the serotonin receptors which cause vasoconstriction and inhibit the release of a whole bunch of neurotransmitters including CGRP and others.

And then there's newer medications that you've probably seen commercials for if you don't pay for premium Hulu like me, like Ubrelvy and Nurtec, these medicines are specifically inhibitors of that CGRP peptide that we talked about. And then we'll talk in the current event section about other modalities that have come up and how much research is being done. Yeah. None of these treatments are perfect but there are a lot of options. So Erin, tell me how did we get here? How do I even ask that question?

Erin Welsh

Yeah, how do I even answer it? I guess we'll find out after the break.

Erin Allmann Updyke

Okay.

TPWKY

(transition theme)

Erin Welsh

Migraines. What are they? What causes them? Who gets them? How do we treat them? Don't worry, Erin, I'm not going to ask you to redo the entire biology section. You're like wait, I thought that I was done.

Erin Allmann Updyke

I answered some of those.

Erin Welsh

Yeah. So you already gave us the answers to what we know or what we think we know about migraines today. But the answers to all of those questions like whether or not aura has to be present for something to be considered a migraine or whether migraines are caused by vascular or neurological changes or if they have a physiological basis at all, those are not going to be the same throughout the history of migraine. And how those answers evolve can tell us more about what was going on in the medical field or even society more broadly than it can tell us about the pathophysiology of migraines, to be honest. It can tell us about what new ideas were popular at certain times or what new discoveries were made, like for instance when allergies or allergens were first identified as a concept, many physicians thought hey, maybe migraines are caused by allergens and they tried desensitization as a result, like allergy shots. Or when hysteria was a popular diagnosis, it was you bring this on yourself and the advice was just don't be so stressed out, don't be so overworked if you want to prevent migraines, like just don't work so hard.

Erin Allmann Updyke

Chill out, bra.

Erin Welsh

Just chill out. Yeah. Or when you're finding earthworms crop up as an ingredient for migraine treatment, that's a sign you're probably in the medieval period in Europe. We'll get there. Humans have always tried to explain diseases or other phenomena within the bounds of whatever knowledge we currently have. And the way we treat those diseases is heavily influenced by popular ideas about what their causes are. We still do that and it's easy to lose sight of that, that our current perception of migraine is only the latest in a long line and is subject to change and likely will change hopefully for the better. But before you can tell us about what those positive changes might be, let's first go back to the early history of migraines so we can see just how far we've come.

Erin Allmann Updyke

Love it.

Erin Welsh

At least in some ways. And I want to give a huge shout out to the book that I used as my primary source for this history section and that is 'Migraine: A History' by Katherine Foxhall. It's a great read and I'll definitely be quoting from it. It shouldn't surprise you, given just how incredibly prevalent they are, to learn that migraines have been known about, written about, experienced, treated for thousands of years. You can find mentions of migraines in basically any ancient medical text from any part of the world. The Ebers Papyrus from around 1550 BCE describes extreme pain in one half of the skull that should be treated by anointing the head with the skull of catfish fried in oil or fat for four days.

Erin Allmann Updyke

Of course.

Erin Welsh

I don't know if that meant fried for four days or just like anointed. I'm guessing anointed for four days.

Erin Allmann Updyke

I would have guessed fried for four days. So that's fascinating.

Erin Welsh

Oh okay. In Ancient China, migraines were treated with acupuncture. In Ancient Greece, bloodletting. And while it has been often suggested that trepanning was done throughout the ancient world to relieve the pain during a migraine specifically, so trepanning like drilling a hole, cutting a hole into your skull, there isn't really much in terms of evidence supporting that it was specifically for migraines.

Erin Allmann Updyke

It's for Dust. Everything I know about trepanning is from 'The Golden Compass'.

Erin Welsh

And trepanning was definitely done but whether or not it was for migraines, probably we'll never know. If anything, trepanning was used specifically for migraine more in the 20th century than in ancient times, at least as far as we know.

Erin Allmann Updyke

Okay, okay.

Erin Welsh

Of course I can't leave the Hippocratic texts out of this. And it's in these texts from the 5th century BCE that we find our first clear description of migraine with aura. A young man, Phoenix, with quote "flashes like lightning in his eye, usually the right. And when he had suffered that a short time, a terrible pain developed towards his right temple, then in the whole head and then into the part of the neck where the head is attached behind the vertebra and there was stretching and hardness around the teeth. He kept trying to open them, straining. Vomits, whenever they occurred, averted the pains I have described and made them more gentle. Phlebotomy helped."

Erin Allmann Updyke

Okay.

Erin Welsh

About 500 years after this description, Galen originated the term 'hemicrania' to describe a condition, a syndrome really, it wasn't like considered a disease, it was more of a syndrome I guess, where half of your head was in pain and sometimes associated with stomach disturbance. Hemicrania turned into 'emigrainia' in Latin and Middle English and then to 'migran' in Medieval Welsh and then to 'magrine'. And then we see all sorts of variations like megrim, migrime. Like the spellings are all over the place.

Erin Allmann Updyke

All wonky.

Erin Welsh

Yeah. And the French word 'migraine' began to be used more widely in medical literature starting around the 1870s. So yeah. And the widespread use of these names for migraine and all of the variations of these names, I think it clearly shows that migraine was not some obscure condition, it was highly recognizable and extremely common. But what was it? What did people think caused it? Erin, I'm sure you can guess what the leading hypothesis for the cause of migraines from like ancient times until I don't know 1700s or so.

Erin Allmann Updyke

Something like humors being off.

Erin Welsh

Yes. I knew that all my talk of the humoral theory of disease has paid off. I've talked about it so much, I feel like this season especially. Yeah, basically an imbalance in humors. In the case of migraine, it was attributed to an excess of bilious humors, yellow bile in youth and black bile in adulthood. And so it follows then that treatment involved getting the humors back into balance. For example, consider this somewhat complicated treatment, aren't they always, from an old English medical text called 'Bald's Leechbook' from 950 CE. And I want a copy of this.

Erin Allmann Updyke

Me too.

Erin Welsh

Quote: "For ache of half the head, take the red nettle of one stalk, bruise it, mingle with vinegar and the white of an egg, put all together, anoint therewith. For a half head's ache, bruise in vinegar with oil the clusters of the loris, smear the cheek with that. For the same, take juice of rue, wring on the nostril which is on the sore side. For a half head's ache, take dust of the clusters of laurel and mustard, mingle them together, pour vinegar upon them, smear that with the sore side or mix with wine the clusters of laurel. Or rub fine in vinegar the seed of rue, put equal quantities of both, rub the back of the neck with that."

Erin Allmann Updyke

Are those like all just different options that you have available to you?

Erin Welsh

Yeah.

Erin Allmann Updyke

Wow, okay.

Erin Welsh

Right?

Erin Allmann Updyke

Yeah.

Erin Welsh

And okay, so first of all there is actually a logic behind these ingredients because in general with the humoral theory of disease, you were supposed to treat a condition with ingredients that had the opposite qualities of that disease.

Erin Allmann Updyke

Okay.

Erin Welsh

So if migraine was thought to be a cold, moist condition, you would prescribe dry, hot ingredients like nettles and mustard seed.

Erin Allmann Updyke

Okay.

Erin Welsh

Why so very many options? Again, there's a reason for it. Not all plant or animal ingredients would have been available year round. If a recipe calls for fresh nettle and you're in the middle of winter, like where are you going to get that? Or even if you just run out, right.

Erin Allmann Updyke

Yeah.

Erin Welsh

And the availability of ingredients would have also changed as trade became more widespread and more herbs and spices were introduced.

Erin Allmann Updyke

Right.

Erin Welsh

Which I think is so interesting to think about, like you can sort of track how trade influenced home remedies for certain conditions over time.

Erin Allmann Updyke

Yeah, that's super interesting.

Erin Welsh

Yeah.

Erin Allmann Updyke: And the seasonality part too. Yeah.

Erin Welsh: So let's see what kind of creative solutions people came up with. So one from 13th century Wales is to quote "eat a baked or roasted hare's brain stuffed with rosemary flowers followed by sleep." Endquote.

Erin Allmann Updyke: Uh-uh. I mean don't do that. I still feel like from our prions episode, just don't eat brains.

Erin Welsh: Don't eat brains. That's a pretty good rule.

Erin Allmann Updyke: Yeah.

Erin Welsh: Yeah. Yet another remedy, not sure where it's from, quote: "We anoint the temples, nostrils, and pulsating veins with rosewater together with the milk of a woman who is nursing a male child and we induce sleep." Endquote.

Erin Allmann Updyke: Ooh, okay.

Erin Welsh: Yep. How about that? Gargling with all sorts of mixtures of things and bloodletting were also really common treatments. And which side of the body you bled from and how much and what time of day, what time of year, all of these things could be adjusted to treat migraines specifically, which I think is interesting to think about.

Erin Allmann Updyke: It's really interesting. I also kind of wonder with bloodletting, like how much blood, I've wondered this for a while, like how much blood would they let, number one? And I actually wonder if there would be any benefit if you let out enough that then you had vasoconstriction. That seems like a bad plan.

Erin Welsh: Yeah.

Erin Allmann Updyke: I just kind of wonder.

Erin Welsh: So I can't remember, I have come across actual quantities but I don't remember anything at this point in time and I think it was pretty variable.

Erin Allmann Updyke: Yeah. It just feels like you would have to do a lot for it to have any kind of effect.

Erin Welsh: Yeah. And then you're just inviting a whole host of other problems.

Erin Allmann Updyke: Yeah, anemia, etc.

Erin Welsh: Yep.

Erin Allmann Updyke: Okay.

Erin Welsh: Okay. But besides bloodletting, which was actually really common, another oddly common ingredient was what I mentioned earlier, earthworms.

Erin Allmann Updyke: Yeah, what?

Erin Welsh
Okay. Quote: "Take six spoonfuls of the gall of an ox or cow. Put thereto two spoonfuls of the powder of the long worms of the earth and the powder of half a nutmeg grated. Boil all of these together upon a chafing dish of coals until it be so thick as you may spread it upon a cloth, then take a double linen cloth and cut it fit for your forehead and as it may cover the temples. Spread this upon it and lay it to your forehead lukewarm and let it lie until it do fall off itself." So in case you missed it, ground up earthworms, the long worms of the earth, made into a paste that you put on your forehead.

Erin Allmann Updyke
Yeah. With some like goat and cow parts too.

Erin Welsh
Cow gall, yeah.

Erin Allmann Updyke
Yeah.

Erin Welsh
Why?

Erin Allmann Updyke
Why?

Erin Welsh
Why? You can find earthworms in all kinds of remedies for things like constipation, jaundice, fevers, or other diseases of the head and brain like throughout the medieval period. Again, why?

Erin Allmann Updyke
Yeah.

Erin Welsh
And I feel like we've come across so many of these very strange to us combination of ingredients and we're just like ha ha, how weird, moving on. But in this book was the first time that I've actually come across an explanation for why earthworms, for example.

Erin Allmann Updyke
Okay.

Erin Welsh
There is a reason. And honestly I kind of like it, I think it's very interesting. Earthworms, because they live in the dirt feeding on rotten matter, were believed to also eat or consume the rotting matter in your body that caused whatever disease you had.

Erin Allmann Updyke
Huh.

Erin Welsh
And so if migraines were caused by like rotting or toxic or putrefied stuff in your head, then that earthworm paste in theory would have eaten up the putrefying matter.

Erin Allmann Updyke
Huh.

Erin Welsh
Yeah. And earthworms weren't alone in this, like other creatures that were quote unquote "bred of putrefaction", like earwigs and snails, were also often used in remedies to like get the toxins out of you. Putrefaction, yeah.

Erin Allmann Updyke
Okay.

Erin Welsh

Up through the late 1700s or so, it seems like the vast majority of these migraine treatments, with the exception of bleeding, consisted of recipes that you could make at home with ingredients that you could find relatively easily. And that's evidenced by the fact that migraine treatments found their way into many home remedy books during the 1500s and 1600s, also showing once again how common migraines were. In one there was even a diagnostic tool where you were supposed to be able to, like I didn't quite understand it, but it was like how much I think of your hand or your thumb you can fit into your mouth.

Erin Allmann Updyke

What?

Erin Welsh

During a migraine. Because if you can't fit however many knuckles in, then you had a migraine.

Erin Allmann Updyke

Because you couldn't like open your mouth?

Erin Welsh

Open your mouth wide enough, yeah.

Erin Allmann Updyke

Interesting.

Erin Welsh

Yeah. The author of 'Migraine: A History' pointed out another interesting aspect of migraine treatments from the medieval and beyond times, which is that while the diversity of treatments both in terms of methods and ingredients for migraines seems completely never ending, they all share one feature. There are no magical or religious elements in them. Migraines had a physical basis and were treated as such.

Erin Allmann Updyke

That's fascinating.

Erin Welsh

Yes, it is. Because it didn't stay that way.

Erin Allmann Updyke

Yeah, I can imagine. Because I feel like migraine has so much similarity to things that we've covered in the past that absolutely did not have the consideration of a real physical basis.

Erin Welsh

Right? It's so amazing to me given the stigma and the shame and the bias surrounding migraines today, even though we know that there is physical basis for them, how much disregard, how much dismissal there is when for the vast majority of its history from ancient times through the early to mid 1700s or so, the prevailing medical beliefs around migraines didn't change all that much. It had a physical basis, it came down to humors.

Erin Allmann Updyke

Wow.

Erin Welsh

Yeah. But like we've seen with many other diseases, especially chronic diseases that we've covered on the podcast, like asthma and epilepsy come to mind, once medicine became more centralized and commercialized, as people moved into cities in the late 1700s and into the 1800s, perceptions of migraine began to shift. It started with patent medicines, taking the 'home' out of home remedy and making concoctions available for people to purchase and doctors to patent and prescribe. Then as hospitals were increasingly built and high population densities in cities meant that doctors could see really orders of magnitude more patients in a year than in past times, they started to observe more about migraines, how frequently they occur, how long they last, what age they usually first happen, the range of symptoms.

And armed with these new observations, they began to draw conclusions about who was getting migraines and why. Were migraines just a cost of social progress in temperance, sedentary lifestyles, lack of restraint, urban living, all of these things, the negative side of social progress were thought to contribute to the rise of quote unquote "nervous conditions". Something that we've absolutely talked about on the podcast in terms of at least gout and asthma. Essentially the view was that as society grew more corrupted, so did our bodies. Was it a wandering uterus perhaps? Probably. Was it being too creative? Could be.

Erin Allmann Updyke

What?

Erin Welsh

Yeah. Not getting a break from the kids or being afraid to delegate household chores?

Erin Allmann Updyke

Oh god.

Erin Welsh

Sure. I know, right?

Erin Allmann Updyke

I boil.

Erin Welsh

Yep. The perception of migraine, at least among the people writing about them, male physicians of course, shifted from a legitimate medical condition with a real physiological basis, even if it was thought to be humoral imbalance, to first a social and then later on a personal failing. And part of this was ironically because physicians were paying more attention to this condition and taking note of other symptoms like GI upset or dizziness, as pain as the primary feature took a backseat. The delegitimization of migraines in the late 1700s and throughout much of the 1800s shifted who was responsible for managing this condition. It was no longer the doctor that had to figure out the correct course of treatment, it was now on the person themselves. If only they didn't overeat, if only they ate at more normal times, if only they didn't drink as much, didn't laze around as much, didn't work so hard, exercised more, exercised less, studied more, studied less, slept more, were less ambitious, were less sensitive, less feminine, stronger, then maybe, just maybe they wouldn't bring this on themselves.

Erin Allmann Updyke

Oh okay.

Erin Welsh

I know, I know.

Erin Allmann Updyke

I'm not surprised by it but it's still upsetting.

Erin Welsh

Very upsetting, I know. What had once been a humoral imbalance was now a nervous disease. And I'm not talking about like a neurological disease that we think of today, I'm talking about the 19th century idea of a nervous disease of which there were many different types. And nerves could be affected by any number of things according to these physicians. And these things and thus the nerves themselves were more under a person's control. But those things, what things affected nerves, of course depended on the person. And with this increased attention on migraines, physicians began to split them up into different types, often gendered. For example, so-called anemic migraines affected quote "mothers in the lower classes of life", endquote, whose bodies were quote "hourly drained by lactation", endquote. But don't worry, if you were a woman in a higher class, you could still get a migraine, just called neuralgic headache, which were quote "undoubtedly hysterical", endquote, in origin.

Erin Allmann Updyke

Aye aye aye aye aye.

Erin Welsh	But also it was just the domestic life in general that gave women so many migraines. Quote: "The anxious forecasting and much serving which slowly undermined the nervous energies of many wives and mothers." Endquote.
Erin Allmann Updyke	Both wives and mothers.
Erin Welsh	Working class men got migraines after being exhausted from quote unquote "excessive hours of labor" or working in the quote "unwholesome and ill ventilated workshops and dwellings of our crowded towns", endquote. But for men of a somewhat higher social grade, it was generally using your brain too much, like reading too much, writing too much, working in legal chambers or the counting house. Too much competition, the excitement of the university and professional life, the anxiety that came from too much ambition, and so on. It could be literally anything.
Erin Allmann Updyke	Aye aye aye aye aye.
Erin Welsh	But it's always the person's fault. And the remedies for all these different types of migraine were fairly straightforward, a break from the stressors which could include maybe a more nutritious diet, not working or studying as much, or for an overworked mother, a forced absence from the home. Yeah, that happened.
Erin Allmann Updyke	Okay.
Erin Welsh	And they're just like you're afraid to delegate, there's tons of people that can help out with your kids, like just leave them. And whether or not any of these things were practical, like let's say that you are working in one of these factories, it's not like you could just be like oh yeah, let me just take some days off work.
Erin Allmann Updyke	Right.
Erin Welsh	No problem. I'll take a vacation to the countryside where the fresh air, the fresh sea air will do me good.
Erin Allmann Updyke	It's not like they were able to use this for like unionizing efforts and actually getting better working conditions.
Erin Welsh	Absolutely not.
Erin Allmann Updyke	Yep.
Erin Welsh	Yeah. But these practical things didn't matter to the physician prescribing them, right? And the physicians prescriptions, by the way, were not limited to changes in lifestyle. The rise of hospitals and other medical institutions like asylums provided ample opportunities for physicians to test out experimental treatments, just the latest and greatest including opium, potassium bromide, arsenic, quinine, and cannabis, which was actually a favorite among many doctors and patients. But nothing reliably worked as I'm sure you could guess. And contributing to this lack of meaningful progress in migraine research, at least in terms of treatment, through the late 19th and into the 20th century, was the lack of certainty in diagnosis. As a quote unquote "invisible illness", people with migraine could appear healthy even in the midst of a horrific attack, which made it easier for physicians to dismiss their pain or not take it seriously, with some physicians saying that someone who is in that much pain can't be relied upon to recount their experiences accurately.

Erin Allmann Updyke

Okay.

Erin Welsh

Not sick enough to be considered chronically ill but not well often enough to be healthy, something like that. It was just like middle ground. Pain as a subjective experience couldn't be trusted by these physicians as the sole diagnostic criterion for migraine. And so they turned to aura. Visual disturbances had long been associated with migraine but hadn't really been studied in a systematic way until the mid to late 1800s, when two scholarly men, British mathematician, astronomer, and chemist Sir John Herschel and physician Hubert Airy presented their experiences of quote unquote "ocular spectra" at a couple of scientific meetings. They described disruptions in visions that could be induced by the shining of a strong light and a quote "singular shadowy appearance", endquote, that sat at the corner of vision and then came into full view with kaleidoscopic colorful geometric patterns.

Airy also shared a drawing of his visual disturbance which he called hemianopsia. And his drawing, which was jagged swirling lines on a black background, became one of the most famous and recognizable illustrations of migraine aura which had become front and center in migraine diagnosis and research as debates continued about whether the condition had a vascular or neurological basis and effective treatments were of course still nowhere to be found. And that's how things remained for the first decades of the 20th century. The pain from migraines took a backseat to aura which had become romanticized, especially with people claiming all sorts of historical and religious figures must have had aura and migraine because their religious visions or drawings resembled aura. Hildegard of Bingen, if that's how you say it hopefully, a saint who lived in Germany in the 12th century was foremost among these and has been called the patron saint of migraines. And really her retrospective diagnosis kicked off a whole bunch more including Moses, Ezekiel, Daniel, St. John the Divine, Charles Darwin, Pablo Picasso, Rudyard Kipling, Virginia Woolf, etc.

And I don't know the details of what went into each of these retrospective diagnoses, like what symptoms did they use? I think for Picasso they just looked at his drawings and they were like yeah, sure. Like did he ever write about pain? Anyway. And of course it is possible that several or even all of these people had migraines. Migraines are incredibly prevalent after all. But the problem with these retrospective diagnoses was how they were used by some people to push this message, which was that A) visual aura was the defining feature of migraines, and that B) people who had the most extreme visual disturbances with migraine were the quote "clever intellectual people endowed with the creative type of mind", endquote. Yeah. And it furthered this idea of there being a quote unquote "migraine personality" which had evolved from the gender and class stereotypes of the late 19th century. Prepare yourself.

Erin Allmann Updyke

Oh dear.

Erin Welsh

According to the American physician Walter Alvarez from the mid 20th century or so, the typical migraine patient was female, quote: "tense, perfectionist, hypersensitive, easily fatigued, and often depressed or disconnected." Endquote. They also had bad periods and quote unquote "defective and poorly functioning pelvic organs".

Erin Allmann Updyke

What?

Erin Welsh

But don't worry, she was also quote "decidedly feminine and sexually attractive".

Erin Allmann Updyke

Ew, ew.

Erin Welsh	But with a masculine vibe that quote "causes her to act independently and to think dispassionately, much as does an able businessman." Endquote.
Erin Allmann Updyke	I cannot.
Erin Welsh	I know, I know. I hate it so much.
Erin Allmann Updyke	Oh my god.
Erin Welsh	Alvarez went so far as to claim that he could spot a migraine patient without even talking to them.
Erin Allmann Updyke	I don't like this guy, straight up.
Erin Welsh	And he wasn't alone in his ideas. There's many people you can dislike. In the 1948 book 'Headache and Other Head Pain', author and neurologist Harold Wolff wrote that his migraine patients had as children been quote "delicate, shy, withdrawn, and obedient to their parents", endquote, but also stubborn. And as adults, they were quote "unusually ambitious and preoccupied with achievement and success." Endquote.
Erin Allmann Updyke	Unusually ambitious.
Erin Welsh	Unusually ambitious. They had a hard time delegating, they were impatient and resentful, cold and aloof. Women brought on migraines by not adapting well to situations like going on vacation. Just like relax, you can't relax on vacation? You're gonna get a migraine, you're gonna give yourself a migraine.
Erin Allmann Updyke	I want to highlight that you said a book from 1948. That was not long ago.
Erin Welsh	No.
Erin Allmann Updyke	Yeah. Okay.
Erin Welsh	Another physician from around this time wrote that people with migraines had quote "a personality that seeks and creates stress and a physiology that handles it poorly." Endquote. So yeah.
Erin Allmann Updyke	It's really interesting because there's evidence now that some of the things that people have historically or even maybe personally identified as potential triggers or things like quote unquote "stress", etc, may actually be part of the prodromal phase of a migraine itself. So it's really even more frustrating to hear these, oh you're causing your self stress. It could genuinely be that people's brains are increasing certain stress responses or something in a way that's entirely outside of your control.
Erin Welsh	Yeah. Well of course.
Erin Allmann Updyke	And then a migraine follows. Like it's just, yeah.
Erin Welsh	As though like all of these things are under someone's control anyway.

Erin Allmann Updyke

Right.

Erin Welsh

Like be less stressed. Try not to worry so much. Just like don't worry.

Erin Allmann Updyke

That advice has helped no one ever.

Erin Welsh

No. And so when you're met with this kind of dismissal and blame from someone who is supposed to be giving you health care, whom you are paying for health care, whom you look to as an expert, how are you going to feel comfortable asking for help? It's so frustrating because like I said, for the vast majority of human written history, migraines were handled as real medical problems with the physical basis, only to have that undermined by physicians who were probably projecting their own insecurities over not being able to effectively treat migraines or define them. And I have no doubt that contributing to this was the gender distribution in migraines, with women much more likely to experience them.

This dismissive attitude towards migraines, the idea of a migraine personality, aura taking center stage as a symptom, we're still feeling all of the effects from this today. And there's a book that I didn't get a chance to read for this episode but I really want to read called 'Not Tonight: Migraine and the Politics of Gender and Health' by Joanna Kempner that goes into this in much more depth and I'll link to it on our website. But this downplaying of migraines as just really bad headaches and sort of the casting off of pain, like dismissing pain as the feature for most migraines, has contributed to the gap in research funds for migraine treatments and the lack of general awareness around the cause and especially the impact of migraines.

They can be debilitating, incapacitating, excruciating, even with stress control, whatever that means, even with sufficient sleep, even with taking a break from the kids, even with medication, even with doing whatever else a doctor tells you not to do so that you don't bring this on yourself. You can't. I'm just so frustrated and I can't help but feel that doctors in the late 19th century and early 20th century, they took one look at migraine and thought I don't know what this is, I can't treat this, therefore it must not be real, or at the very least it must not be as bad as they say, or it's probably a personal failing on their part because I'm a trained medical professional and I can't admit that I don't know something or can't treat something.

Let me read you one final quote from a physician and then I'll get us off this rage train maybe. In 1902, JM Aiken wrote in JAMA that quote "of all the common and much dreaded nervous diseases we recognize, none are less perfectly understood than migraine. Nor is there any other nervous disorder which is so disastrous to the physician's ability for treatment. It is easy to say what migraine is not but difficult to define what it is." Endquote.

Erin Allmann Updyke

I mean even just the framing of that as like this is hard for doctors.

Erin Welsh

Oh yeah. And I didn't even get into some of the gendered advertisements from the mid 20th century for migraine treatment where it's like geared towards doctors that are like it's not just a problem for your female migraine patient, it's also a problem for you. Kind of implying like she's complaining to you and she keeps seeking help, so prescribe her this.

Erin Allmann Updyke

Wow. Oh wow.

Erin Welsh

It's good stuff. Yeah. In the second half of the 20th century, we did make substantial progress in understanding what migraine was, especially with the introduction of the international classification of headache disorders in 1988. We made progress in what caused it with the neurological framework sort of overtaking the vascular one and then kind of being integrated with this new neurovascular framework. And we also made progress, a lot of progress in how to treat it, first with the introduction of ergotamine and then like Migril tablets which was a combination of ergotamine, caffeine, and cyclizine introduced in the 1950s. And then also another treatment that you mentioned which was introduced in the 1980s was the triptans, with the first one being sumatriptan. And so we've come a long way in our understanding and prevention/management of migraine. But we clearly have so far to go still, not just in treatments and making those treatments accessible for everyone who needs them, but also in reducing stigma, shame, and blame surrounding migraines. Like believing people. What a concept. Why is it so hard? Why is pain the most dismissed thing?

Erin Allmann Updyke

I feel like we talked about this in our endometriosis episode a lot as well.

Erin Welsh

Yeah, yeah. Also hugely gendered aspect there.

Erin Allmann Updyke

Because you can't see pain, like when we talk about being able to measure something, right.

Erin Welsh

Right. But we also can't see aura.

Erin Allmann Updyke

Yeah, that's true.

Erin Welsh

Or like nausea.

Erin Allmann Updyke

But you can see vomiting.

Erin Welsh

You can see vomiting. Yeah.

Erin Allmann Updyke

Yeah.

Erin Welsh

I think that I spent so much time sort of in the earlier history of migraines because I really did want to get across the point that we used to be better at this. I mean yes, it was the humoral theory of disease but it was like oh here's this real thing, here are some real treatments for it.

Erin Allmann Updyke

Yeah.

Erin Welsh

Oh but maybe it's not real, maybe it's all in your head.

Erin Allmann Updyke

Yeah.

Erin Welsh

And it's just so many diseases are like this that we've covered on the podcast. We've talked about asthma, we've talked about lupus, we've talked about epilepsy, we've talked about of course endometriosis, that have undergone this shift that I think coincides with when medical knowledge was increasing overall but not necessarily shedding any light on those conditions. And so rather than saying maybe it's something that we don't know about yet, it had to be put in this box of maybe it's in your head. I'm sure that we'll look back on this period of time with similar diseases that right now are classified as psychosomatic or whatever it is. Anyway, I'm at the very end of this, I've gone on this rant and now I should just stop myself and turn it over to you, Erin.

Erin Allmann Updyke

I love it, Erin. I mean I hate it.

Erin Welsh

Oh yes. So where do we go from here?

Erin Allmann Updyke

Ooh, okay, okay. Let's take a break, take a breath, and we'll find out.

TPWKY

(transition theme)

Erin Allmann Updyke

Migraine is estimated to affect 1 billion people worldwide depending on the paper that you read and what data you use, meaning if you consider definite and probable migraines based on those ICHD criteria, that's between 15% of the global population or as high as 35% of the general population having migraines each year. 35%, Erin, if you include probable migraine.

Erin Welsh

And that's every year, that's not lifetime.

Erin Allmann Updyke

So this is, yeah, annual prevalence.

Erin Welsh

Wow.

Erin Allmann Updyke

It's not incidence, we don't have great data on incidence. But that's annual prevalence. Now across all age groups, prevalence of migraine is significantly higher, usually 2-3 times higher depending on age in people who are assigned female at birth compared to people assigned male. And prevalence tends to peak usually in the 30s but really age 25-40. So this is young people being very significantly affected. Among people with active migraine, the median monthly attack frequency, so how many episodes of migraine per month is 1.5. But a quarter of people have weekly attacks. And remember that the total duration of a migraine attack can last up to a week.

Erin Welsh

Oh my gosh.

Erin Allmann Updyke

Right? And up to 5% have chronic migraine which again means 15 headache days a month, 8 of which meet criteria for migraine. So with all of that being said, it should come as no surprise, though this was shocking to me, the World Health Organization ranks migraine as the most prevalent disabling long term neurologic condition, period. And it's not necessarily because it's the most common. Even in terms of headaches, tension type headaches are far more common than migraine. But migraine is so disabling that as an example, while tension type headache affects almost a billion more people worldwide, like 800 million more people than migraine, migraine causes six times as many estimated disability adjusted life years or years lived with disability.

Erin Welsh

Whoa.

Erin Allmann Updyke

Migraine in 2018 caused an estimated 45 million years lost to disability, compared to 7.2 million for tension type headache.

Erin Welsh

Oh my gosh.

Erin Allmann Updyke

And the data hasn't changed much over the years. That estimate was from a 2018 paper based on 2016 data. Based on 2019 data, it's an estimated 42.1 million years lost to disability. It's obscene.

Erin Welsh: Yeah.

Erin Allmann Updyke: Especially because we have treatments. Migraine is the leading cause of disability worldwide for people younger than 50 years, especially for women. And I don't want to just go based on disability adjusted life years or years lost to disability because we know that that's an imperfect metric. But I also have read that in studies that have looked based on survey data, from the US at least, on people's reported effect on their lives, that up to 30% of people who live with migraines say that it affects their careers in some way, 30% say that it affects their parenting in some way, and nearly 50% feel that it affects their relationships.

Erin Welsh: Yeah.

Erin Allmann Updyke: That's huge.

Erin Welsh: It's huge.

Erin Allmann Updyke: And caveat that those numbers are based on US data, so we don't know the universality of that but I mean this is not a minor disorder to live with.

Erin Welsh: Right. And just living with that uncertainty and that unpredictability.

Erin Allmann Updyke: Yeah.

Erin Welsh: And planning. How can you plan around a migraine when you don't know if you're going to have one?

Erin Allmann Updyke: Yep, exactly.

Erin Welsh: Oh my gosh.

Erin Allmann Updyke: If you're more interested in money and cost, in Europe financial costs that are attributed to migraine are estimated at between \$50 billion to \$111 billion. And that was like 15 years ago. And what's interesting is that in Europe, the vast majority of that cost is estimated to be indirect cost, meaning not healthcare dollars but dollars lost in other ways because of lost productivity at work, etc. Whereas in the US, direct costs are estimated at \$11 billion annually and indirect cost \$12 billion annually.

Erin Welsh: Wow.

Erin Allmann Updyke: So there's a lot of discrepancy there. I'm sure there's a whole podcast about that. So migraine is a massive issue. And most of the data that we have on migraine come from Europe and the US and high income countries. But migraine is a global phenomenon that affects people across the entire world. And in low and middle income countries, not only do people tend to lack access to a lot of treatment or even diagnosis options, people are far less likely to be diagnosed accurately with migraine in low and middle income countries, we also have much less data to guide policy and to guide programs. And part of this is because the focus tends to be in low and middle income countries on other additionally pressing health issues, things like TB and HIV which are more common in low and middle income countries. But that's despite the fact that migraine is also causing massive amounts of disability in these countries as well.

Erin Welsh	Right.
Erin Allmann Updyke	And there's estimates from a whole bunch of different countries that indirect costs alone can be as much as 2% of gross domestic product annually.
Erin Welsh	Whoa.
Erin Allmann Updyke	Because of migraine.
Erin Welsh	Yeah.
Erin Allmann Updyke	So when it comes to current research, it's a little hard for me to even know where to begin.
Erin Welsh	Is that a good thing?
Erin Allmann Updyke	I don't know.
Erin Welsh	Okay.
Erin Allmann Updyke	Sometimes in this section I'm able to say here's this one new great thing that just happened or is on the horizon and it's about to happen. I don't have that one great thing for migraine.
Erin Welsh	Okay.
Erin Allmann Updyke	But that's not because there haven't been great strides made in migraine research. There have been a number of really new drugs in the last year, really this year in 2023, and in the last couple of years that have come down the pipeline. There have been new monoclonal antibodies that specifically target this CGRP pathway and many of which are intended to be used as preventative treatment. So especially for people who have chronic migraine or just a high burden of migraine each week or each month, even if they don't meet criteria for chronic migraine. Preventative rather than just what are called abortive treatments or treatments made to be used when a migraine happens, right. And there have also been other oral medications that includes that whole class called the gepants which are the ones that have commercials right now like Ubrelvy and Nurtec. I probably shouldn't use brand names but whatever. These are things that also target that CGRP peptide. There's also a brand new nasal spray that targets the same peptide.
Erin Welsh	Fascinating.
Erin Allmann Updyke	I know. And there's a relatively new, I think in 2019 was when it was approved by the FDA, was a medicine in a class called ditan which are very similar to triptans but they have less vasoconstrictive effects, which means less cardiac risk and therefore more people can probably use it.
Erin Welsh	Cool.
Erin Allmann Updyke	And then there are really creative things like botox injections, trigger point injections, neuromodulatory mechanisms, and probably a bunch more drugs coming down the pipeline as well. But there isn't a silver bullet and a lot of that is because there's still just so much that we don't know when it comes to migraine.

Erin Welsh

Yeah.

Erin Allmann Updyke

So some of the other big areas of research besides just therapeutics are things like identifying biomarkers, either blood biomarkers or imaging biomarkers, things that we can identify on an MRI that can either predict the risk of migraine or predict treatment targets so that we can develop even other types of therapeutics. But in general, there's a lot of mixed results when it comes to a lot of things with migraine research but especially with this attempt at identifying various biomarkers. I think the thing that gives me hope is I will say that when I was researching for this episode, I found more very recent papers in well regarded journals about migraine research than I have found for any of our recent episodes.

Erin Welsh

Oh wow, okay.

Erin Allmann Updyke

Like a lot. There's a whole series that came out in The Lancet three paper series that came out in 2021. There's Nature papers and New England Journal papers, a lot of kind of high profile research that's really, really recent when it comes to migraines. So that gives me hope that it's getting a lot more attention because we are recognizing what a massive issue it really is. That's migraine.

Erin Welsh

Gosh, I hope we did it justice, Erin.

Erin Allmann Updyke

Yeah, is that enough? I don't know.

Erin Welsh

I don't know. I don't think so.

Erin Allmann Updyke

Tell us.

Erin Welsh

Could it ever be enough?

Erin Allmann Updyke

No.

Erin Welsh

Luckily there's more reading.

Erin Allmann Updyke

There's so much more. Let us tell you about it.

Erin Welsh

I'm going to shout out again 'Migraine: A History' by Katherine Foxhall and I'll link to it on the website.

Erin Allmann Updyke

I have a lot of sources for this episode. A few that I loved were 'Migraine: A Primer' from Nature Reviews Disease Primers in 2022. There was also a paper titled 'Migraine and the trigeminovascular system: 40 years and counting' from The Lancet Neurology in 2019. Also I mentioned already but there's a great series, it's three different papers about different aspects of migraine from the epidemiology to disease characterization, like biomarker research, and approaches to management and emerging treatments that all came out in The Lancet 2021. We'll have a list of this and all of our sources from this episode and all of our episodes on our website thispodcastwillkillyou.com under the EPISODES tab.

Erin Welsh

We certainly will. A big, huge, tremendous, incredible thank you to everyone who shared their experience, their story with migraine. We really can't thank you enough.

Erin Allmann Updyke

Yeah. Thank you. Thank you also to Bloodmobile for providing the music for this episode and every one of our episodes.

Erin Welsh

And thank you to Lianna Squillace for the amazing audio mixing.

Erin Allmann Updyke

Thank you to the Exactly Right network.

Erin Welsh

And thank you to you, listeners. We hope that you, I don't know, got something out of this episode, learned something, I don't know.

Erin Allmann Updyke

Yeah, I hope so.

Erin Welsh

Let us know. We appreciate you.

Erin Allmann Updyke

And a special shout out as always to our patrons. Thank you so much for your continued support. We really appreciate it.

Erin Welsh

Yeah, thank you. Well until next time, wash your hands.

Erin Allmann Updyke

You filthy animals!