



MIGRAINE WORLD SUMMIT

# TRANSCRIPT

INTERVIEWS WITH WORLD-LEADING EXPERTS

BRAIN-RELATED COMORBIDITIES OF MIGRAINE

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**Introduction** (00:05): Well, I want to thank everybody for teaching us: We, as researchers, scientists, healthcare professionals, need to hear from you all the time. And as Michael J. Fox says, the person living with the disease is the expert. *You* are the expert. So if you think there might be a comorbidity, you think there's a symptom that might be related, please let your healthcare professional know because it really might be, and we just haven't done the research to uncover it yet.

**Elizabeth DeStefano** (00:34): We know that migraine has a number of other medical conditions connected to it in some way. If we have migraine, then we are more likely to have these other conditions, including brain-related disorders. Each of these comorbidities presents their own unique challenges, and their combination with migraine involves important considerations for treatment plans. We're fortunate to be joined by Dr. Dawn Buse to discuss migraine's intricate connections to these neurological comorbidities. Here we'll explore the interplay between migraine and conditions like epilepsy, multiple sclerosis (MS), fibromyalgia, stroke, insomnia, and mood disorders. Dr. Buse, welcome back to the Migraine World Summit.

**Dr. Buse** (01:18): Thank you, Elizabeth. I'm really happy to be here. And hello to everyone watching this video.

**Elizabeth DeStefano** (01:23): Dr. Buse, what is a comorbidity?

**Dr. Buse** (01:27): Well, comorbidity means that two or more conditions or diseases occur at higher rates than they would by chance. So, when we think about chance, we can think about 50% — a little bit more — of the population are women. And maybe a certain percent have brown hair. And we can say, "Well, are those occurring together more likely than they do by chance?" And in fact, it's a no for that one. I would call that a co-occurring condition. But when the likelihood of one means that the likelihood of the other is going to be there, that's a comorbidity. So these are things that travel together.

**Elizabeth DeStefano** (02:05): What are the most common comorbidities of migraine?

**Dr. Buse** (02:09): So, we already have quite a few clusters of known comorbidities. There are psychiatric comorbidities. That's going to be depression, anxiety, panic disorders, suicidality, nonsuicidal self-injurious behavior. As well as cardiovascular comorbidities, respiratory comorbidities, neurologic comorbidities, comorbidities related to sleep, and some other types of comorbidities.

**Elizabeth DeStefano** (02:35): What links these comorbid conditions to migraine?

**Dr. Buse** (02:40): Well, maybe it's chance; maybe it's the being female and having brown hair. Maybe it's just these two things happened. Or maybe one causes the other. Maybe I light a piece of paper on fire in my fireplace, and then I have a fire. That match [and] that lighter lit the fire. Now I have a fire. That seems pretty obvious to go one direction. Or maybe things go two different directions. Each increases the chance for the other. Or maybe there's a third or a bigger underlying reason. Some of those reasons might be shared genetics or genes. Two things that run in families. It might be shared environment. For example, not having your basic needs when growing up, malnutrition, adverse childhood experiences. Or on the opposite end, having everything — having enough healthy food and water and shelter and health insurance and access to medical care. So it might be environment. It might be shared neurologic pathways, shared neurotransmitters, shared things happening in the body that are related to two or more diseases.



**Elizabeth DeStefano (03:49):** How are depression and anxiety identified?

**Dr. Buse (03:52):** When it comes down to it, you're probably your best expert. You know these feelings, but of course we do have criteria because we always need to figure out a way to document and really confirm that someone indeed meets a diagnosis. Depression, feeling sad, down, hopeless, or helpless. Probably doesn't surprise you, but the number two criterion, which is so important to think about, is anhedonia. That is when you just don't feel like doing things that you used to enjoy. "An" meaning not, and "hedonia" meaning pleasure. You're not getting pleasure out of life anymore. There [are] about nine questions that your doctor may ask you. We often start with those first two, then we go to the full nine, and then we can make a clinical diagnosis of depression.

**Dr. Buse (04:37):** After we make that diagnosis, there are many subtypes of depression as well as severity. Is it mild? Is it moderate? Is it severe? Is it so severe that there is suicidality or thoughts of hurting oneself involved? Of course, we want to act on that right away. And the one reason that that level of severity is important in migraine is, in fact, we found that not only were people with depression who had episodic migraine one year more likely to have chronic migraine the next year, we found that the risk of increasing actually increased with the severity of depression. Now we go back to, does one cause the other? Do they both cause each other? Is there a shared underlying reason? We can't say what direction things are going there. It may be that overall, this kind of disease state and the state of the nervous system, maybe inflammation in the body is kind of increasing and it causes both of those conditions to kind of increase ... maybe a hypothesis that's possible and it's related to certain parts of the brain.

**Dr. Buse (05:46):** Anxiety. Anxiety shares, surprisingly, a lot of the criteria for depression diagnosis — a lot of those — kind of feeling restless, nervous, on edge. But let's start with the first two hallmark symptoms. Is it difficult to control your worrying? Do you find you're worrying about a lot of things? You can't turn off that worry? Those are kind of your general anxiety symptoms, and we'll definitely know that when we feel it. We're going to find rates in the general population of about 20% — 1 in 5 people with episodic migraine having depression, anxiety, or both. And then it goes up to about 30, 35% — about a third of people with chronic migraine in the general population have depression, anxiety, or both. So a lot of things happening here with depression, anxiety, and amount or frequency of headache days. We also found in our MAST study — the Migraine in America Symptoms and Treatment study — that when we ask people, "What's your average pain intensity?" for an average migraine headache phase — that zero to 10 scale — that the rates of depression, anxiety, as well as other things — insomnia, epilepsy, and about a dozen things — increased with that average headache pain intensity.

**Dr. Buse (07:05):** And one good news piece — I've got to give you some good news because this is all sounding bad — is that as migraine frequency reduces, so does depression and anxiety. So you can just see how tied together they are. These are like two grumpy old guys on a bus. These guys travel together. Or the three of them — they're really a triad. They're Larry, Curly, and Moe there with the depression, anxiety, and migraine, for probably a variety of reasons. Shared genetics: They travel in families; they're all related to inflammation in the body; they're all related to the nervous system. They're involved with some of the same neurotransmitters. They involve some of the same parts of the brain as well as just the kind of human experience that living with a chronic, unpredictable, painful, debilitating disease that hits you like a tsunami every so often is just awful and it makes you feel depressed. It makes you feel hopeless and helpless about your future and your condition, and it makes you worry about a lot of things.



**Dr. Buse (08:09):** So, there's also that real logical part of, "This is hard, and these are my feelings." We just want to treat all of them. Treat all of them. Treat all of them appropriately with medication, with the healthy lifestyle habits that always matter, with the nonpharmacologic approaches like biofeedback and CBT [cognitive behavioral therapy]. We want to treat them all. So, when we want to get our treatments reimbursed, we're going to need those diagnoses in the chart and may need to have those criteria filled out. As well, it's really nice to track changes in mood. And so, it's really great when you do get a questionnaire, an instrument from your healthcare professional to complete, and you get a number score; it just gives you a general idea from visit to visit how you're feeling now versus how you were feeling then.

**Elizabeth DeStefano (08:55):** But if we're sitting at home really struggling to manage living with migraine — understandably — and realizing that we have some of those symptoms that you mentioned as hallmarks of depression and anxiety, it may not be ... serve us best to debate whether those are really things that need to be focused on, or rather just when we're feeling particularly burdened by migraine. Rather, discussing those and being open with those, knowing that addressing them regardless is an important part of our improvement.

**Dr. Buse (09:28):** Thank you for mentioning that, Elizabeth. It's true that while depression and anxiety are so common, they're actually more common than *not* having them when you live with chronic migraine or even frequent episodic migraine. They're highly stigmatized, and I think we all take it upon ourselves to feel kind of guilty and embarrassed by feeling these symptoms. And yet they're based on neurotransmitters, neurochemical levels in the brain, genetic predispositions. They're as real of a disease as anything else is. And the good news is they do respond to treatment, and it does not have to be medication. They respond really well to cognitive behavioral therapy approaches, mindfulness approaches, biofeedback, as well as some of our important healthy lifestyle habits that also help migraine. So, healthy sleep hygiene, staying hydrated, eating healthy, keeping a healthy weight, exercise and movement, and stress management. These actually really help depression, anxiety, and migraine. So, I hope people don't take that label upon themselves if they're feeling any of these feelings. Know that it is part of the experience of migraine. It's incredibly common, and they are treatable.

**Elizabeth DeStefano (10:44):** Thank you for that, Dr. Buse. Now, what is epilepsy?

**Dr. Buse (10:50):** Epilepsy is a chronic brain disease where there's abnormal activity in the brain. And that abnormal electrical activity in the brain leads to seizures. So just like we think about migraine as a chronic disease with episodic manifestations or migraine attacks, epilepsy is also chronic disease with seizures or episodic attacks from this abnormal activity. The abnormal activity can manifest in quite a few different ways, from convulsing, or shaking, or clenching of muscles, difficulty talking, difficulty with movement, feeling of numbness, tingling, and usually is a distinct episode that happens pretty quickly and is over in a number of minutes usually and it's out of the blue. So of course, this is a very scary disease to experience, and it can be really disturbing to people experiencing it [because] they don't know when it's going to happen and it's impossible to function when an attack happens.

**Elizabeth DeStefano (11:47):** How do epilepsy and migraine relate to one another?

**Dr. Buse (11:51):** Well, epilepsy and migraine are comorbid. We think that people with epilepsy are about twice as likely to have migraine as people without. So, in the U.S., we think about 12 to 15% of people have migraine, and among those who had epilepsy, the rates are about 24%, so about a quarter of people.



**Elizabeth DeStefano (12:13):** It sounds like something that migraine and epilepsy share in common is a brain hyperexcitability, if you will. It also seems that females are disproportionately affected with these conditions. Are there any other similarities that are of interest in their comorbidity?

**Dr. Buse (12:34):** Well, they also share more comorbidities, and I talked about those comorbidity clusters. So they also share more comorbidities, like depression, can join in the triad there. As you mentioned, yes, the preponderance amongst females being a little bit more frequent for people with epilepsy. And then we actually see an even higher comorbidity rate among adolescents. Epilepsy can happen at any age, and among children and adolescents, they're more likely if they have epilepsy to also have migraine, and it's associated with more symptoms of epilepsy.

**Elizabeth DeStefano (13:11):** A member of our community asks if epileptic seizures are triggered by a migraine attack. Can treating that migraine attack earlier effectively prevent that risk of epileptic seizure?

**Dr. Buse (13:26):** So, if someone has frequent migraine, there's a good chance that a seizure may happen at the beginning or during a migraine. It's a little hard to tell if one is causal of the other, but of course there are shared underlying brain hyperexcitability activities going on. Although a little bit different in epilepsy, there's activation of many neurons at once. Whereas in migraine, we have this cortical spreading depression (CSD) — more like a row of dominoes — so they're a little different. But what I want to say is that scientists and clinicians are aware of it, and we're trying to figure it out. And please document what happens to you because what you feel is real and what you experience is our best data. So please continue sharing with us.

**Elizabeth DeStefano (14:12):** Multiple sclerosis is another long-term, potentially very disabling brain-related disorder. What is MS, and how does it relate to migraine?

**Dr. Buse (14:22):** Absolutely. So, in MS, the body's immune system attacks the protective sheath, or myelin, that covers nerve cells, and the nerve cells need that myelin to submit or transmit communications to different muscles in different parts of their body. So when that myelin is attacked or eaten away, the brain cannot communicate with parts of the body, including muscles; the ability to walk; or the ability to talk; including vision, [which] can sometimes be affected; and many other systems of the body. As you mentioned, MS is a long-[term] chronic illness after it's diagnosed. It often starts in midlife, mid-adulthood, but it can start younger, and it has two different courses. It may be a relapsing and remitting, so the symptoms occur and get worse for a while, and then they might return to baseline or at least remit to some extent. And there's also a chronic, primary progressive form.

**Elizabeth DeStefano (15:27):** Now my understanding there from what you've said is that multiple sclerosis can change for some people with the condition over time, just as migraine can increase or decrease in frequency. Do migraine attacks increase for someone with multiple sclerosis during MS flares?

**Dr. Buse (15:50):** That's an important question, and there's plenty of clinical evidence suggesting that during an MS flare, in fact, someone will have more frequent migraine attacks, perhaps more intense symptomatology, or just experience more distress from the attacks. Of course, everyone is different, and so different people will have different experiences with MS as well as different experiences with migraine.



**Elizabeth DeStefano (16:16):** How much more likely is someone to have one of these conditions if they have the other, when we're talking about multiple sclerosis and migraine?

**Dr. Buse (16:26):** Well, they absolutely are comorbid, and people with MS are 3 to 4 times more likely, depending on which research study we look at, to also have migraine.

**Elizabeth DeStefano (16:37):** Another chronic condition that affects many in the migraine community is fibromyalgia. What is fibromyalgia?

**Dr. Buse (16:44):** Fibromyalgia is a chronic disorder that causes pain and widespread tenderness throughout the body and is also associated with fatigue and difficulty sleeping, as well as other symptoms.

**Elizabeth DeStefano (16:56):** How do fibromyalgia and migraine relate to one another?

**Dr. Buse (17:01):** Well, they seem to be bidirectional. And it may not be that one causes the other, but it may be that both are kind of in the predisposition and that either one can manifest first. So when someone has migraine, we'll see fibromyalgia in about 20 to 36% of people with migraine. And if we look at it on the other side of the coin, among people with fibromyalgia, we see migraine in about 50 to 80% of those with fibromyalgia.

**Elizabeth DeStefano (17:30):** In considering symptoms of fibromyalgia and migraine, what similarities and differences exist?

**Dr. Buse (17:38):** Well, thinking first about the epidemiology, they're both a bit more common in women; they both can occur in men. Migraine tends to start pretty early in life, whereas fibromyalgia tends to come on in the early to midlife years. Fibromyalgia is more chronic in that someone tends to feel those pain and fatigue symptoms most of the day every day, whereas we know that migraine for many people will have an episodic nature in that attacks come and go. Although for some people with migraine, they may live every day with headache.

**Elizabeth DeStefano (18:14):** And what role might central sensitization play in both [of] these conditions?

**Dr. Buse (18:21):** Central sensitization is actually a key factor in both of these conditions. It happens when the body's nervous system gets activated or wound up and stays in that space. And one way we know it's happened is when all of our senses are really on high alert, and we'll talk about light kind of hurting. We'll see people with migraine or fibromyalgia wearing glasses even indoors, wearing sunglasses, wearing hats, trying to stay out of the direct sun. Also, everyone listening is probably familiar with either sounds being too loud or painful; or smells causing distress, pain or nausea; as well as allodynia, which is when something that's normally not painful, such as a touch to the skin, hurts. Allodynia is when your ponytail hurts or wearing a hat, or a headband hurts. It's that light touch to the skin that's not normally sensitive is sensitive. All of those are related to central sensitization of our nervous system, and they're related to both migraine as well as fibromyalgia.

**Elizabeth DeStefano (19:25):** We've been speaking of a number of chronic conditions. Now let's touch on one important acute emergent condition: stroke. What is stroke?



**Dr. Buse (19:35):** Yes, stroke is a medical emergency. It is damage to the brain that has happened from interruption of the blood supply. It happens immediately, quickly, in an instant. And you may have headache that feels like the worst headache of your life, thunderclap headache. It also has other symptoms, often weakness, which may be on one side of the body, numbness. You might see a drooping of the eye, the mouth, the face. Of course, difficulty speaking, talking, maybe difficulty standing up, and difficulty understanding and comprehending. In stroke, time is of the essence. You need to get someone to the emergency department as fast as possible. Call 911 immediately.

**Elizabeth DeStefano (20:25):** Let's talk about important similarities and differences between stroke and migraine.

**Dr. Buse (20:30):** Well, living with migraine, we know, is an intensely painful headache. These thunderclap headaches that one might feel during stroke is going to feel even much worse than that. In addition, all of the symptoms of stroke are going to come on instantly and rapidly and come on together. Whereas we know with a migraine attack we have the 24 hours of prodrome, we have our 5 to 60 minutes of aura, which might be those symptoms that match up, line up with stroke a little bit, and then followed by the headache. And in that case, that headache is a bit reassuring because it's kind of our normal path of migraine. The aura symptoms of a migraine are going to be those that most closely potentially mimic stroke symptoms, but they're going to come on more slowly. They're going to spread over 5 to 60 minutes, and then they're going to resolve before the headache. The stroke is very dramatic, as a migraine aura can be. And I think for people who regularly experience migraine aura, they may have a sense of what their aura typically looks like and feels like, and that can be a bit of a comfort; as distressing as it is to know, "This looks like my typical aura," versus different symptoms that may feel even more debilitating and be unusual symptoms.

**Elizabeth DeStefano (21:57):** A lot of our viewers wonder and worry about migraine increasing stroke risk. What can you share about the data on this association?

**Dr. Buse (22:09):** So, there's a real[ly] important difference between absolute risk and relative risk. And absolute risk is: How often does stroke happen for women in midlife and younger? Very, very, very, very, very rare. So when we double that by two, it's still very, very, very, very rare, doubled by two. Even when we look at our highest increased rates for a woman in midlife who has migraine with aura, who is taking oral contraceptives and is overweight (BMI) and is a smoker, and we increase our risk of stroke eight times, it's still eight times very, very, very, very rare. So I don't want people to be scared generally about the risk of stroke in migraine for women who are younger to midlife, but it is something to think about. We do have a couple modifiable risk factors.

**Elizabeth DeStefano (23:02):** What about medication selection for migraine?

**Dr. Buse (23:07):** For migraine, we're going to think about if someone has a high risk or has had any type of cardiovascular history — a heart attack, a stroke, anything like that. The triptans are contraindicated, and those are what we use acutely, that are migraine-specific medication taken at the time of the attack. So it's really important to let your migraine healthcare provider know if you have risk factors for or have had any cardiovascular events. So the triptan, for example, that maybe you were taking in your 20s or your 30s may need to be reevaluated 10, 20, 30 years later. Especially, as we mentioned with oral contraceptive use, for someone who is a smoker, for someone who has a higher BMI. And especially if they have had a cardiovascular incident, an MI [myocardial infarction], a stroke, you tell your headache doctor right away, or your primary care



[physician] or your neurologist, whoever's taking care of you, right away. Because they will modify your medications based on that.

**Elizabeth DeStefano (24:08):** You introduced us to this idea of groupings of conditions, including as you've mentioned in a number of cases, insomnia. What is insomnia?

**Dr. Buse (24:18):** Insomnia actually can happen at different times during the sleep schedule. It could be the beginning of falling asleep; it can be the middle; [or] staying asleep. Or it can be waking too early and having a difficult time going back to sleep. We call those early, middle, and late insomnia. Insomnia basically is difficulty initiating or maintaining sleep. And we find actually that those different phases coordinate with some of the different diseases. For example, people with anxiety may have a harder time falling asleep, whereas people with depression tend to wake too early and may have an impossible time or very difficult time going back to sleep. So slight differences in how insomnia manifests.

**Elizabeth DeStefano (25:01):** What are other common sleep disorders?

**Dr. Buse (25:04):** Sleep disorders that are comorbid with migraine also include restless leg syndrome and sleep apnea, as well as a couple other more exotic, less common sleep diseases and sleep disorders.

**Elizabeth DeStefano (25:17):** And how much more likely are we to have insomnia or another sleep disorder if we do have migraine?

**Dr. Buse (25:24):** Well, in the MAST study — the Migraine America Symptoms and Treatment study — we found that people with migraine were almost four times as likely to have insomnia as those without migraine.

**Elizabeth DeStefano (25:35):** A recent review in the journal *Neurology* highlighted that migraine, just like cluster headache, is highly circadian in nature. What implications does that have for migraines linked to sleep disorders?

**Dr. Buse (25:50):** Yes. The research shows that for people with migraine, about 50% of attacks are related to these circadian patterns. And in fact, there's a circadian pattern where there's a lowering of melatonin between about 11 p.m. to 7 a.m. for people, which tends to be a time that they might be more at risk of an attack. And so, people who say, "I get those morning migraines; I wake with them, or they wake me up, or I wake up and they're already going," are affected by that trough that happens late night to morning. In addition, there's some annual seasonal circadian patterns as well that affect humans, and we'll see that people with migraine have that pattern between about April to October that also might be affecting their migraine patterns. And in cluster headache, we'll see that spring and fall potential for more attacks, as well as also a late-night peak as well.

**Elizabeth DeStefano (26:51):** So, having now spoken about a number of conditions, what considerations are important when managing treatment of migraine with any comorbidities, specifically those we've focused on today?

**Dr. Buse (27:05):** Well, two things I want to say. One, please don't feel bad, guilty, embarrassed, or anything. Let's bring down the stigma. Life with migraine is life with comorbidities. This is a constellation of comorbidities that is incredibly common. In fact, if you don't have any





comorbidities, then you are the most rare unicorn — rainbow unicorn — because almost everyone's going to have comorbidities. So it's normal. So please don't take it upon yourself personally. As we said, it has to do with all sorts of genetic predispositions, neurotransmitters, inflammation, things happening systemic in the whole body — as well as external forces, environmental and social — all sorts of things that have gone on to create this constellation of comorbidities that you might experience along with migraine or other types of headache diseases. That's No. 1.

**Dr. Buse (28:02):** No. 2, you can see how important it is that your healthcare professional knows about it. Don't be afraid. Please share all your symptoms with your healthcare professional caring for migraine. And because there might be a link, it might inform how they're going to treat you to make sure that they're treating you safely. So, one, don't be embarrassed; not your fault. Two, let your healthcare professional know. Three, there are some data that look like when one of these conditions gets better, the others might as well too. They kind of travel together. So, it's a good thing to actively treat as many of your comorbidities or at least monitor for safety as possible.

**Elizabeth DeStefano (28:45):** What final thoughts would you like to leave with our community, Dr. Buse, on neurological comorbidities or brain diseases that accompany migraine?

**Dr. Buse (28:56):** Well, I want to thank everybody for teaching us: We, as researchers, scientists, healthcare professionals, need to hear from you all the time. And as Michael J. Fox says, the person living with the disease is the expert. *You* are the expert. So if you think there might be a comorbidity, you think there's a symptom that might be related, please let your healthcare professional know because it really might be, and we just haven't done the research to uncover it yet. So please don't feel stigmatized, or embarrassed, or guilty, by anything you experience when you live with migraine.

**Elizabeth DeStefano (29:33):** And where can we learn more about you, Dr. Buse, and the work that you do?

**Dr. Buse (29:38):** Well, one thing I think that everyone with migraine may want to do is know that you can go right to the source at any time. You can go to PubMed, P-U-B-M-E-D, right online at any time and read the abstract of any scientific article. That way, you can actually read it for yourself, interpret it yourself, and kind of keep up to date. So that is always open and available. Secondly, of course, you're already listening to the Migraine World Summit. This is an amazing resource for education. So you can't go wrong by educating yourself, which is so empowering and so helpful. And if anyone would like to learn more about me or practice relaxation exercises, they can find me on my website, which is just my name: DawnBuse.com.

**Elizabeth DeStefano (30:26):** Wonderful. Thank you. And Dr. Buse, thank you so much for everything you have shared in covering the intricate relationships between migraine and associated neurologic comorbidities. Thank you so much for being here. We appreciate you.

**Dr. Buse (30:42):** Thank you, Elizabeth. And thank you to everyone listening. Be well.