

INTERVIEWS WITH WORLD LEADING EXPERTS



WHY MOST DOCTORS GET THE DIAGNOSIS WRONG

ROBERT COWAN, MD



Introduction (00:05): General physicians and even neurologists have very little training in headache. Even though it's the most common neurologic complaint in the emergency room, most physicians are not well trained in it. At best, they may have kind of a general idea that, you know, bad migraine ... bad headaches are migraines and trivial headaches are tension-type. And then they're heavily influenced by pharma as to which medications to prescribe. I would venture to say that underdiagnosis is as much of a problem as misdiagnosis.

Carl Cincinnato (00:39): Less than half of us with migraine go to the doctor, and from those who go to the doctor, less than half again receive an accurate diagnosis. Why are patients and doctors seemingly getting this so wrong? To help us understand these questions and many more, we have Dr. Robert Cowan from Stanford Medical School. Dr. Cowan is the chief for the Division of Headache Medicine, where they use an interdisciplinary approach to headache treatment. On staff are several board-certified headache specialists, nurse practitioners, psychologists, and physical therapists. Dr. Cowan is heavily involved in research and is actively publishing new research findings and conducting lectures internationally at headache conferences to raise awareness to educate clinicians and patients. Dr. Cowan, welcome back to the Migraine World Summit.

Dr. Cowan (01:24): Thank you. It's good to be back.

Carl Cincinnato (01:26): Does everyone with migraine go to the doctor?

Dr. Cowan (01:28): Oh, no. Not by a long shot. Part of the problem is when you have a headache, you need help right away. And when you don't have a headache, you don't think of yourself as sick or needing help. As a result, many, many patients go to the emergency room when they have a headache and only bring it up kind of at the end of a visit to the doctor. We call it a doorknob diagnosis. As they're leaving the office, they say, "Oh, and by the way, I have these headaches," and the doctor says, "OK, we'll talk about that next time."

Carl Cincinnato (01:59): So why wouldn't someone go to the doctor to get diagnosed if they have migraine?

Dr. Cowan (02:05): Part of it is the stigma of migraine. It's not considered a real disease by many people. And it's the old excuse, "I can't because I have a headache." But it's actually a genetic disease, migraine is, and it really is best treated by a physician and their support team.

Carl Cincinnato (02:31): For people who have episodic migraine — so migraine that's not chronic, it's not terribly frequent, it might be one or two a month and it may not be that severe — is it necessary that they go to the doctor?

Dr. Cowan (02:41): Not necessarily if they genuinely only have infrequent headaches and they're adequately treated with over the counter medicines — that's fine. The problem is, like most diseases, if you don't treat them appropriately, they get worse. And two headaches a month can quickly creep up to a headache every week and then two headaches a week. And before you know it, you have what's called chronic migraine, which is headache more days than not.

Carl Cincinnato (03:09): There was a study done by the Mayo Clinic a couple of years ago with Dr. Dodick and others that showed that for people that have chronic migraine — so



frequent attacks that may be disabling — the rate of consultation to a clinician was still below 50%. Is that concerning?

Dr. Cowan (03:30): Yes, it's very concerning. The problem for us as headache specialists is that delay in treatment and in diagnosis makes it much more difficult for us to take care of the patient when they do arrive. They've been started on medications inappropriately. They've been given wrong diagnoses like a sinus headache or tension-type headache. It's more of a challenge for us as clinicians. And of course, it's a lot of suffering. On average, it takes about 18 months to get the correct diagnosis and be seen by someone who is knowledgeable in headache, and it can cost about \$12,000, not to mention the time missed from work and from family activities and things like that.

Carl Cincinnato (04:15): So those are a couple of reasons why a diagnosis is important. Are there any other factors that you think are important to mention?

Dr. Cowan (04:22): Part of the challenge is the diagnosis itself. It wasn't until 1989 that we even had criteria for diagnosing headaches. And one of the problems we see is that two people can come in and be properly diagnosed with the same condition, say episodic migraine, and yet one will respond beautifully to one medication and the other won't respond to it at all. So one of the challenges we have is getting better at diagnosing within the diagnosis, understanding those subgroups of people with episodic migraine who are going to do well with behavioral therapy or going to do well with medicine A or medicine B.

Carl Cincinnato (05:02): And there's not just one type of migraine. There's many.

Dr. Cowan (05:06): Yes, yes, there's ... well, there's the distinction between episodic and chronic, which is purely numeric. And that's a little misleading in and of itself. It's useful for research, but I'm much more concerned about the patient who's gone from four headache days a month to nine headache days a month than I am for the patient who's crossed that line from 14 headache days a month to 16, which would move them from episodic to chronic. But there are hemiplegic migraine and complicated migraine. So there are other rarer types of migraine ... migraine with aura, migraine with the brain stem aura.

Carl Cincinnato (05:44): So if someone has one type of migraine, let's say it's migraine with aura, for example — which affects 30% of people with migraine — why can't that 30% of people with migraine all go to a doctor or all get the same treatment and get better? Because we see that in other conditions like with pneumonia, for example.

Dr. Cowan (06:01): Perfect example. If I tell you you have pneumonia and I test a sample of your sputum and I see that there's a bug there and I can put that bug into a petri dish and give an antibiotic, see if it kills it. If it does, I can treat it. If three months later or 20 years later you still have the same infection, you probably should have had that diagnosis revisited. And that happens with pneumonia. It doesn't happen with migraine. We see patients all the time who've been given a diagnosis, for example, of chronic migraine, and yet they've tried everything that we have for chronic migraine and haven't responded. When we go back and start over and take a very careful history, a very detailed history, we find actually that they have a spontaneous intracranial pressure problem where their intracranial pressure is either too high or too low. So getting the right diagnosis is critical at the beginning and sometimes you just have to start over and listen carefully to what the patient's telling you.



Carl Cincinnato (07:04): We talked about a couple of different types of headache. Some patients or people that have been told they have migraine might be told that they have a subtype of migraine. Is that referring to some of the different types of migraine? What are migraine subtypes?

Dr. Cowan (07:19): So it's probably better to take one step back from that. There's two broad categories and that is primary headaches and secondary headaches. Secondary headaches are headaches that are due to some other condition. Primary headaches are not easily attributable to an infection or to a head trauma but within the primary headaches, we have three categories. We have migraine, we have what they call trigeminal autonomic cephalalgias — which are things like cluster headache or SUNCT ... SUNA; there's several of them. And we have tension-type headache. So, the first challenge is to determine whether it's a primary or secondary headache. If it's a secondary headache, you go after the cause. If it's a primary headache, you need to differentiate within those three broad categories. But for a clinician ... and that's useful for headache research. But for a clinician, there's only one patient sitting in front of you and their headaches are unique. And that's kind of what we focus ... that's how we work at Stanford anyway.

Carl Cincinnato (08:24): How many different types of headache are there?

Dr. Cowan (08:27): Well, there's 60 million people in this country with headache and every one of them is unique. So, when you're talking about a clinical diagnosis, you can parse it however you choose. For example, myself, I could eat chocolate until I was 300 pounds. It does not trigger a headache for me. I have patients who can't even walk by the chocolate counter without it triggering a headache. Are those two different kinds of migraine? Probably not. But we all have different triggers and we all have different thresholds for what's going to trigger a headache. And so I think as a clinician or as a patient, it's not so much ... it's not so important to distinguish between the recognized classifications because they're too broad. They don't give us guidance.

Carl Cincinnato (09:19): What condition is migraine commonly mistaken for, or what conditions?

Dr. Cowan (09:25): Probably the most common is something like sinus headache. And the reason for that is your sinuses hurt and your sinuses hurt when you have migraine for the same reason that amputees have pain in their foot. You have a cortical brain representation of every part of your body. And when the pain is in that representation, that's the part that hurts. But a sinus headache actually should have disgusting green stuff coming out of your nose and a fever for it to be a sinus headache. But that's probably one of the most common incorrect diagnoses.

Carl Cincinnato (10:01): And we've heard a lot of stories from patients that have said that they've been rushed to the hospital ... having a migraine attack and thinking that they're having a stroke. Have you heard of similar cases?

Dr. Cowan (10:13): Oh, of course. Of course. I'm guilty of that myself.

Carl Cincinnato (10:17): Oh, really?

Dr. Cowan (10:17): I was in medical school. I got a bad migraine and it seemed worse than everything else and anything that I'd ever had before. And it was actually probably the result



of spending a day in the cadaver lab in my anatomy class, but I was sure I'd just had a cerebral hemorrhage. As a medical student, you have ... a dangerous amount of knowledge, right?

Carl Cincinnato (10:41): Yeah.

Dr. Cowan (10:41): And I went and I got a, at the time, CAT scan, because I was sure that I'd had an intracranial hemorrhage. So, yes, when you're hurting, you're scared and if you don't have information — accurate information — and you don't have access to resources, you go to the emergency room. It's one of the reasons that this is such an expensive disease.

Carl Cincinnato (11:05): And it seems to affect so many of our senses that we could easily attribute something wrong with our sense and that being, sort of, being diagnosed with something related to that. So you mentioned sinusitis obviously with our sinuses, but then a lot of people can have vestibular problems and maybe there's an inner-ear issue and they see an ENT and there's a diagnosis there. Have you heard about those, as well?

Dr. Cowan (11:27): Well, of course. I think the best way to think about migraine is it's a problem between the patient and how they interact with the environment, whether it's the internal environment — hormones — or the external ... in my environment, bright lights, loud sounds. And all of your senses can be affected by that. And that's why when you have a migraine and even between migraines, as you chronify — as your headaches become more frequent — loud sounds become more of a problem; bright lights become more of a problem even when you don't have a headache. It's this whole process of sensitization, that goes on. In the same way, if you are camping and you hear a sound, suddenly you're on fire and you're listening for everything. And that's what happens as you chronify with migraine.

Carl Cincinnato (12:14): And coming back to the diagnosis side of things: I remember when I was having migraine with aura, for me personally, I went and saw an optometrist and saw several optometrists and ended up wearing prescription glasses, which I didn't need for several years because I was told that I needed to wear them.

Dr. Cowan (12:31): I remember as a child I had allergy testing. I remember just being tortured with all these pinpricks on my back and being told I could never go on grass. Imagine a child of the '60s never going on grass.

Carl Cincinnato (12:45): Wow.

Dr. Cowan (12:47): But on average, a patient will see three to five physicians before they see a headache specialist. And as you said, it can be an ear, nose, and throat specialist. It can be an anesthesiologist who specializes in pain medicine, an ophthalmologist, a gynecologist. It's a problem.

Carl Cincinnato (13:09): And there's times where migraine can be misattributed when it's actually something else. So, for example, you mentioned, head pressure and high- and low-pressure headaches. That can present as migraine, but it's actually something else. Can you tell us a little bit about that?

Dr. Cowan (13:23): So probably ... one of the hottest topics in headache medicine right now is a condition called a subacute intracranial hypotension. And what happens is some people develop a tiny little leak in the sac that holds the brain and the spinal cord. And as a result,



spinal fluid leaks out as you're standing around during the day, and you feel fine first thing in the morning because you've been lying flat. But over time, standing up and sitting up, the headache gets worse and worse because those cranial nerves are being stretched. You have chronic nausea like you do with migraine. You have visual problems like you can with migraine. And traditionally, the only way SIH was diagnosed was if someone had just recently had a spinal tap and they were ... it was a florid leak. But many people can leak a little bit over many years. And as a result, the autoregulation of spinal fluid production and resorption is altered. And this has been probably one of the most rewarding areas in our clinic in the last few years, are these patients who come in with years of diagnosis with chronic migraine. And when we start to look at the phenotype that's typical for patients who have this condition, we discover that patching that leak is life changing.

Carl Cincinnato (14:59): And what do you mean by phenotype? Sorry, for those that might ...

Dr. Cowan (15:01): So,for example, more typically, patients who have leaks are people who have mixed connective tissue disorders — what we call Ehlers-Danlos spectrum — tall, lean, very flexible. They're those people who can put their palms on the floor and touch their thumb to their wrist. They seem to be more prone to having leaks. People who've been in car accidents. If someone says, "Yes, my headache started right after ... " or "My headaches got worse right after ..." some kind of head trauma or neck trauma, whiplash injury, that raises our suspicion that there may be a leak.

Carl Cincinnato (15:42): So, when you say phenotype, you mean it's almost like a set of characteristics or a profile?

Dr. Cowan (15:46): That's exactly what a phenotype is. It's as distinct from say a genotype, which is your genetic makeup. It's the way a person looks, the way they interact with the universe. Increasingly, we've found that the more data you collect on a patient — and you know, it's no secret; we've known this for a couple hundred years — the more you know about a patient and the more the patient knows about their disease, the better off they're going to be. So, increasingly, we're collecting as much data as we can. And now with computers, it's a lot easier and we can let the data sort out what the problem is.

Carl Cincinnato (16:25): Another condition that is often mixed with migraine — and it can start off as migraine and morph into — is something called medication overuse headache or rebound headaches. Can you tell us about whether this is a primary or secondary condition and if there's a debate amongst clinicians, at the moment, as to how to describe and why this is misattributed?

Dr. Cowan (16:46): Sure. So, medication ... there's no debate as to whether medication overuse is a secondary headache. It's super imposed on the primary headache. Interestingly, for example, people with chronic low back pain can take anti-inflammatories on a daily basis, and they don't get medication overuse headache. But what happens in a migraineur — in people with migraine — is that over time, when you take medication for your headaches, your brain starts to think that's part of the normal chemistry, and it upregulates receptors for those drugs. And when that drug isn't present — like after a long night's sleep — your brain thinks there's something wrong, there's something missing. And the way it communicates that is with pain. And so you take more medicine and you feel better, but it's not treating the underlying headache. So, the underlying headache is progressing and you're taking more medication, which isn't actually treating the primary cause of the headache. And that's how this cascade of medication overuse begins.



Carl Cincinnato (17:54): So, we've talked about migraine being disguised as other conditions like high- and low-pressure headaches, medication overuse just then, and how, often, other conditions can be confused for migraine such as vestibular migraine, sinus or sinusitis, and vision issues. What happens if the wrong diagnosis is given?

Dr. Cowan (18:17): The untreated disease gets worse and then, very often, the elements to treat are not utilized. If you think someone has migraine and you just give them medication after medication for migraine and you don't address the lifestyle issues and the need for a preventive medication, the underlying condition gets worse.

Carl Cincinnato (18:43): There was a recent study done by John Hopkins that suggested that medical errors may be the third most common cause of death in the United States. Are errors any less frequent within migraine?

Dr. Cowan (18:57): They're probably as frequent. They tend to result in morbidity rather than mortality with few exceptions — obviously the opioids can push it right over into mortality really quickly — but it's mostly morbidity. Most medications have side effects, and very often, people with migraine have other comorbidities — other medical conditions — so that you're treating one condition and making another condition worse. So it gets very, very complicated.

Carl Cincinnato (19:31): So morbidity doesn't refer to death.

Dr. Cowan (19:33): A morbidity is suffering and ...

Carl Cincinnato (19:36): ... burden of disease.

Dr. Cowan (19:37): Exactly.

Carl Cincinnato (19:39): Do we know how common misdiagnosis is for people with migraine?

Dr. Cowan (19:44): So, I don't know of any specific data on that. But I can tell you from our clinical experience, it's very common.

Carl Cincinnato (19:56): Would you say a majority of patients that you see in your clinic have been misdiagnosed in the past?

Dr. Cowan (20:01): We have a skewed population because we see patients by referral from ...

Carl Cincinnato (20:06): You see the worst of the worst, right?

Dr. Cowan (20:08): Yes. But certainly, many, many of our patients fall into that category.

Carl Cincinnato (20:13): Why do you think other doctors are getting this so wrong?

Dr. Cowan (20:19): I think there are several reasons. I think general physicians and even neurologists have very little training in headache, even though it's the most common neurologic complaint in the emergency room. And it costs the economy, depending on which studies you look at, between \$15 and \$30 billion a year. Most physicians are not well



trained in it; at best, they may have kind of a general idea that bad headaches are migraines and trivial headaches are tension-type. And then they're heavily influenced by pharma as to which medications to prescribe. I think that's probably a big contributor to the misdiagnosis and the underdiagnosis. I would venture to say that underdiagnosis is as much of a problem as misdiagnosis.

Carl Cincinnato (21:13): How is underdiagnosis different from a misdiagnosis?

Dr. Cowan (21:17): So, when your diagnosis is "it's just a headache."

Carl Cincinnato (21:19): So, it's almost belittling the condition; not giving you the adequate treatment it deserves.

Dr. Cowan (21:25): Exactly. It belittles the condition and it belittles the patient.

Carl Cincinnato (21:29): What can be done to address the level of misdiagnosis within migraine?

Dr. Cowan (21:34): Education, I think, is probably the paramount way to address it, but I also think we need to get better at diagnosing. We talked earlier about those subcategories within migraine. We need to get a better understanding of why one group of patients will respond well to one medication and another group won't respond to it. There's probably something in the phenotyping or in the genotyping that will give us that information.

Carl Cincinnato (22:03): And we've talked a lot about the doctors getting it wrong. Do you think the patient has some responsibility, as well?

Dr. Cowan (22:09): Well, I'm a big fan of patient-centered medicine. I think that one of our biggest challenges is to take that ... we call it the locus of control. Very often, when a patient comes into the office, they want you to fix their headache. And what they really would be better off thinking is they want you to help them fix their headaches. There are lots of things you can do personally that will have a greater impact on their headache ... on the headache than any medicine I can give. So, I think bringing that locus of control back to the patient is really, really important — to understand that there are things you can do to improve your headache condition either instead of, or in addition to, the medicines that we give.

Carl Cincinnato (22:59): Do you think there's a role for technology, as well, to play a role; to play a part?

Dr. Cowan (23:03): I think there's a huge role for technology. I think there's always this issue of ... are doctors going to be replaced by machines? I think that's absurd. That's sort of like saying, "Is the EKG going to replace the cardiologist?" Or, is the stethoscope going to replace the pulmonologist? I think the medicine is so complex. I mean, there are ... I forget the numbers ... but there are hundreds of thousands of articles published daily. I mean, the information is just growing so fast. We can't keep it all in our heads. And any doctor who says they can is probably a little arrogant, but computers have no problem with that. You know, I can ask Siri or Alexis. Alexa?

Carl Cincinnato (23:51): Yes, Alexa. Yes.



Dr. Cowan (23:52): ... Ask Alexa to pull up a song from the mid '60s and they can do it instantaneously. I'd have to search for days to find it. So, I think the power of especially artificial intelligence to take that burden away from the patient, away from the physician and the patient, is tremendous. And I think the sooner we learn to use artificial intelligence and technology to do that part of it — what we would normally do looking up in a book — the more time we'll have to actually listen to the patient and to get to know the patient and gain some insight into the things that doctors are supposed to do well, which is show some compassion. So, show some attention and actually help the patient along.

Carl Cincinnato (24:40): Some people may have heard of Watson, the IBM supercomputer that has medical implications and supports doctors in diagnosis and in decision support. Is this what we're talking about ... sort of developing a Watson for migraine?

Dr. Cowan (24:55): So, I don't ... well, I do want to trash Watson, but I won't. I think the approach that Watson uses, is this compendium of knowledge that is basically using a computer to be a really smart guy or gal. Excuse me. And what I'm talking about is really artificial intelligence. Let me give you an example from some work we're doing. We are collecting kind of random data — or apparently random data — on patients where we ask anywhere between 40 and 450 questions of a patient who has headache. And it's questions about sleep, it's questions about exercise, it's questions about, their emotional state, their other comorbidities or other medical conditions, what medications they've taken, whether they stopped it because they didn't work or because they had side effects. And we just collect all of this information and it all stores. And we have an algorithm that takes all of this information and groups it. So, in other words, we can almost say we can ... if we have 10 or 20,000 or 100,000 patients who all have a diagnosis of episodic migraine, the computer can start to break them down into ... Well, look at this group: they all have a good response to topiramate or to Ajovy or to something. And they also all seem to have low anxiety scores. Isn't that interesting? I wonder if there's a connection? There are things that we wouldn't see in the, you know, 10 to 20 patients we might see in a day, but the computer can look at 100,000 patients and begin to see categories. So you start to get an understanding of which patients might be more likely to respond.

Dr. Cowan (26:53): A lot of us do that intuitively after practicing medicine for 20, 30, 40 years but this can actually be quantified. And that's sort of the power of artificial intelligence. So, it goes beyond just collecting information, specifically requested, which is basically what Watson does. And it goes on to learn more. What it does is it'll take 80% of the people that seem to be in a group and then test it on 20% and then take a different 80% and test it on 20%. And it'll do that hundreds of thousands of times. And little by little, you start to find these groups that all seem to ... an example I can give you is we compared imaging, functional imaging, in people who don't have any headaches and people who have chronic migraine. And interestingly, we found that patients who have chronic migraine have a larger amygdala on one side than the controls.

Dr. Cowan (27:58): So, then we go back and we look at the testing that we've done, and we collected information on something called catastrophization. And catastrophization is what I say, "We're going to try this" and the first response is, "Well, what if that doesn't work?" or, "I can't go to a movie because what if I get a migraine?" And we found, interestingly, that these people with big amygdalas on one side scored higher on catastrophization than the controls did. Now, you don't know whether that's the jockey or the horse ... is the big amygdala causing someone to be anxious and catastrophizing? Or, does catastrophizing lead to the big amygdala? And what's the connection between the headaches? So, now we've got



that data and we've published that data. Now what we're doing is we're looking at people with episodic migraine, and we haven't published this yet, but basically, we're finding that among episodic migraine sufferers, it's kind of a mix. Some of them have high catastrophization scores; some don't. We're doing longitudinal studies to see if, over time, people with episodic migraine, some of them are going to go on to chronic; others won't. I never chronified. If there was wood, I would knock on it. And I don't think I'm much of a catastrophizer so it's an interesting notion. And then we're also looking at some of the ... at these chronic patients that we've imaged and they're being treated and a significant number of them are going back to episodic with appropriate treatment and we're going to see whether their amygdalas shrink.

Carl Cincinnato (29:33): Interesting. So, is this research that's ongoing at the moment? How can people who are watching participate?

Dr. Cowan (29:42): Well, for our research, the best, quickest and easiest way would be to go online and just complete those questionnaires. It's free and all. It's secure, it's anonymous. And what you're doing is helping us build our database, looking for those hundreds of thousands of people to see who classifies where. It can be helpful to an individual patient because the questionnaire will give them a printout that reads like a narrative history, a consultation from a headache specialist giving them a clinical impression and a medical, medicine history. But the real power of it is that it will help us get better at classifying people and figure out who's going to respond to what treatments.

Carl Cincinnato (30:31): Does it replace the need for a doctor?

Dr. Cowan (30:33): No, no, no. It's — again, it's like the stethoscope — it's just a tool and it should not be used without seeing a doctor. I mean ... but it's very useful to bring that very high-level consultation to your primary care doctor and say, "Look what these headache specialists say about my headache. Does this help you in treating my headache?" We found that the primary care doctors and general neurologists are very grateful to have that kind of input. But no, it's not intended to replace the doctor.

Carl Cincinnato (31:06): So, if someone's not able to see a headache specialist but wants to get a professional perspective on their condition, they can take this survey, get a printout, take the printout to their family doctor or a general practitioner and work with them to figure out the next steps and confirm or ...?

Dr. Cowan (31:24): Exactly. Exactly. That was the intent. That's actually why we developed it in the first place.

Carl Cincinnato (31:29): And what happens with people's data that they're using in that research?

Dr. Cowan (31:33): So, that's a big deal. So, we have this thing called HIPAA, which requires that personal health information be protected. So, what we do is we silo the data separate from the person submitting the data so there's no connection. It's kind of like Bitcoin, in a sense. There's no connection between your de-identified data and you except through you. So, you have access to it but no one else does. So we use the de-identified data for our research and the identified data can only be obtained through you, through your email and a password.



Carl Cincinnato (32:16): What do you hope will come out from the research?

Dr. Cowan (32:19): We're very hopeful that we'll get better at figuring out what kinds of patients are more likely to respond to what kinds of treatments. We're also hoping that it will give us some insight into phenotypes that we can tie to genotypes. In the example I gave you, there are specific serotonin carrier proteins that are coded in the amygdala. And we can look at blood — and we're doing this in other studies — and look at the genetics and see whether it's a deficiency or a surplus of this carrier protein for serotonin that is responsible for the amygdala getting big or vice versa.

Carl Cincinnato (33:08): Where can people go to take part in the research?

Dr. Cowan (33:11): So, the public website is called BonTriage.com. And when you go to that site, it's got an app there that's free, which is helpful for studying your headaches and it's got the questionnaire that you can take.

Carl Cincinnato (33:29): Excellent. Well, we'll put a link to that, as well, in the show notes. Dr. Cowan, it was a pleasure having you back at the Migraine World Summit.

Dr. Cowan (33:35): It was a pleasure being here. Thank you.