



MIGRAINE WORLD SUMMIT

INTERVIEWS WITH WORLD-LEADING EXPERTS

TRANSCRIPT



**SAFETY UPDATE: DHE, TRIPTANS,
MAGNESIUM, BUTTERBUR & MORE**

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Introduction (00:05): There's another misconception about drug interaction between triptans and antidepressants like Prozac and Zoloft. There's a warning, actually, that you shouldn't mix them, but it's really not based on any science. And we know for a fact, because a colleague of mine requested from the FDA all the data that they used to issue this warning. And he found that there was not a single case of a patient taking a triptan plus an antidepressant who developed so-called serotonin syndrome. That's the interaction. All of them either had multiple drugs on board or had many other medical conditions.

Elizabeth DeStefano (00:43): In recent years not only do we thankfully have new treatment options for migraine, but also regularly emerging updates about previously existing treatments. Staying on top of it all can be challenging, but so important as we strive for effective and safe approaches to managing migraine. Here to update us on the latest news and safety in a number of treatments, pharmacologic and natural, is Dr. Alexander Mauskop. Dr. Mauskop, welcome back to the Migraine World Summit.

Dr. Mauskop (01:14): Thank you for having me again. It's a pleasure.

Elizabeth DeStefano (01:19): So, clinicians and patients themselves are picking and choosing from a number of different options in treating migraine. There are so many factors to consider — certainly efficacy, but safety is at the top of the list, too. So, let's dive in, in talking about some treatments that we've heard about recently with news around them, starting with DHE. Dihydroergotamine is one of the treatments used in migraine management and it's carried an associated cardiovascular risk warning. Can you tell us why that is and also what the latest research in this area shows?

Dr. Mauskop (01:57): Well, DHE, or dihydroergotamine, is one of the oldest migraine medicines we've had. It's been on the market now for 75 years, so it's a very, very old medicine. But it came out only as an injection. And then, the reason for renewed interest in DHE is that a new nasal spray was introduced that seems to be almost as effective as the injection. So that is why we are talking about DHE again after it's sitting quietly in our drawers. And we still use the injectable DHE for very difficult-to-treat migraine patients. So, if all the treatments fail, we would give someone intravenous DHE. And people often receive DHE in the hospital. When someone's migraines are so severe that they need to be in the hospital, an intravenous course of DHE can break the cycle.

Dr. Mauskop (02:56): So it's a very effective, very strong medicine for migraine. But it has some baggage, and that's what we're talking about — the safety. Unlike the new class of drugs that came after DHE — they're not so new anymore, they've been on the market now 30 years — triptans. Sumatriptan and the others have a much cleaner safety profile. They don't constrict blood vessels as much as DHE, and that's the major concern, that if you give too much DHE, blood vessels constrict. If you have heart disease, it's definitely contraindicated. If you have peripheral vascular disease, many people with migraine will have cold hands and feet, so-called Reynaud's syndrome. And if you give them DHE, their blood vessels can constrict, and it can be a serious, serious complication of losing circulation and even losing digits in extreme cases. So that's the concern.

Dr. Mauskop (03:50): Ergotamine, including DHE, is an effective medicine, but it affects many receptors. The triptans are very selective for a certain type of receptor, 5-HT_{1B} and D we call them. DHE, we call it a "dirty drug"; it affects many different receptors, and intravenously it can cause nausea and vomiting. Fortunately, nasal spray is less likely to do that. So it's a very



effective drug. It's not the first one on the list because of cardiovascular concerns. But on the other hand, the majority of migraine sufferers are young women. For them it's not as much of a concern. As you get older and you have risk factors for heart disease, cardiovascular disease, that's when you have to be more cautious.

Elizabeth DeStefano (04:37): So you mentioned triptans, Dr. Mauskop. In your recent book, *The End of Migraines: 150 Ways to Stop Your Pain*, you list triptans as one of your top three acute drug treatments for migraine attacks. You also describe how underutilized you believe triptans are. Why is that?

Dr. Mauskop (04:58): Well, again, as I mentioned they came out in 1992, the first triptan. Sumatriptan was approved as an injection first. So we have over 30 years now of experience with these medications. And the proof that they are very, very safe is the fact that for more than 10 years now, in most European countries, you can buy triptans without a prescription. You just walk into the pharmacy and ask the pharmacist, and they will give you a triptan. So 30 years is long enough to establish the safety of any product. After four or five years, we still could be unsure. But 30 years is long enough to know everything about the drug. And we have studies looking at literally millions of people who are given that prescription. These are big studies looking at databases, not at each individual patient. And the databases suggest that even if you had coronary artery disease or risk factors for vascular disease, and you took a triptan, it still is remarkably safe.

Dr. Mauskop (06:02): At the same time, the label for these drugs still mentions that if you have coronary artery disease, you should not be taking it. If you have multiple risk factors, you should not take a chance. Now, if someone has two or three risk factors, and I really think they could benefit from a triptan, I will do a basic workup looking at their blood vessels, whether it's a calcium scoring test of coronary arteries or a stress test. And if that's clean, then I still will prescribe the triptan without any hesitation. So, some people have a misconception that if you take it for a long time, you are risking developing heart disease, which is never the case. Only if you have preexisting disease, then you have to be cautious. But again, I tell patients: Ibuprofen or aspirin is much more dangerous, in my opinion, than triptans. Because those we know for a fact cause thousands of people to die from gastrointestinal bleeding, kidney damage, and many other side effects. With acetaminophen, or in Europe it's called paracetamol, you are risking liver problems. So in my opinion, triptans are extremely safe.

Elizabeth DeStefano (07:12): So, those safety concerns can get in the way of someone benefiting from a medication like a triptan. What else interferes with triptan use? For instance, is it possible that someone tries one triptan that they don't respond to, and could respond to another? Or don't use the correct dose of a triptan that would work for them?

Dr. Mauskop (07:34): You're right, all these factors play a big role. So, especially people think that if you try a triptan and it didn't work, you do have to examine the strength of the medicine that you took. For example, sumatriptan is available at 25, 50 and 100 mg. So, I have patients coming and tell me: "I tried it, it didn't work." "How many milligrams?" "Twenty-five." So, for an average person, 25 is not going to work. Sometimes 50 works, but for most of my patients, I begin with 100 mg, unless they're very sensitive to medications, they're very small in size, or children — and we do use triptans in children. And several of them are approved by the FDA in the U.S. for children as young as 8. So we use triptans, and we make sure that patient takes the highest allowable dose, and then we'll decide whether it works or not.



Dr. Mauskop (08:29): And you're also right in that some days one triptan works a little bit or causes side effects. I always suggest trying at least one more triptan. And by the way, there are seven triptans on the market. In the United States we have all seven, and in most European countries, three or four. But that's sufficient. It's enough to try one or two, maybe three. Just this morning I had a patient who said, "Sumatriptan works but makes me tired. I have to take a nap." So we're definitely going to try rizatriptan, naratriptan, eletriptan, and see if — just the fact that they responded to the sumatriptan tells me that their migraine involves serotonin receptors. Because CGRP drugs — new drugs — for some of the patients, those are the magical drugs. For others, they do nothing and sumatriptan is the miracle medicine. So, if someone tells me it worked but caused side effects, or it worked but took a long time, it's definitely worth trying not only other triptans but different forms of triptans. For example, sumatriptan comes in three forms: tablets, nasal spray, and as well as an injection. And the injection is also very underutilized. So, we can talk about the injectable sumatriptan, as well. And I should add that I'm a migraine sufferer, which most of my patients like to hear because I can relate to their experience, and I can tell them I've tried many medicines, and sumatriptan for me is the best one.

Elizabeth DeStefano (10:00): So, how do you decide which delivery system of a triptan to try first with someone who's exploring triptans for the first time?

Dr. Mauskop (10:10): Well, you don't have to decide which one first. I often give patients both the injectable and the oral, depending on the circumstances. So, injection is something you can have for more severe attacks or sudden attacks, or when you wake up with a severe migraine and you have to go to work and take care of the family. So injection is perfect for that. And if it's a slow buildup, and you know there is time for you to take a pill, you take the pill. And the nasal spray is sort of in between — it's intermediate. If you don't like the idea of needles, nasal spray for some people works almost as well as the injection. But for other people it does nothing at all because the nasal mucosa might be inflamed, they might have some allergies, and the absorption through the nose is not consistent.

Elizabeth DeStefano (10:56): So, to summarize safety concerns for triptans, what do you consider?

Dr. Mauskop (11:03): So, the safety is Number one is that if you have coronary artery disease, or you have multiple risk factors such as diabetes, high blood pressure, high cholesterol, smoking, age, then you have to be really concerned. There's another misconception about drug interaction between triptans and antidepressants like Prozac and Zoloft. There's a warning, actually, that you shouldn't mix them. But it's really not based on any science. And we know for a fact, because a colleague of mine requested from the FDA all the data that they used to issue this warning. And he found that there was not a single case of a patient taking a triptan plus an antidepressant who developed so-called serotonin syndrome. That's the interaction. All of them either had multiple drugs on board, or had many other medical conditions. So, millions of sufferers, many millions of migraine patients, have depression because they are — we call them comorbid conditions. It's not that the migraine makes you depressed, it goes both ways. If you have depression, you are more likely to develop migraines. If you have migraines, you're more likely to get depression, anxiety, and other issues. So, many people have to take both an antidepressant and a triptan, and there is not a problem with that combination.

Elizabeth DeStefano (12:26): Well, that's an important piece of safety information, I'm sure, for a lot of our viewers. So thank you for including that. In your book, you also dispute the widely



held idea that frequent use of triptans is a risk factor for development of medication overuse headache, or medication adaptation headache. What can you share with us on that topic?

Dr. Mauskop (12:49): They strongly believe — and I must stress, this is a belief, not based on any scientific fact — that if you use the triptans more often than twice a week, you are running a risk of so-called medication overuse, or rebound headaches. That is, the headaches get worse from the medicine. Well, there's no science behind it. We do have good science showing that caffeine and caffeine-containing drugs, like Excedrin in the U.S., as well as opiate analgesics — codeine, Vicodin, Percocet — we have good data on those making headaches worse. There are many so-called correlational studies looking at — the beginning of the year, if you took lots of triptans, your headaches often become more frequent and you have to take more triptans. This is not necessarily cause and effect, because maybe your headaches got more frequent, more severe, and you need to take more medicine.

Dr. Mauskop (13:44): The typical scenario is, patient comes to a doctor: "Take it twice a week, and that's it." "Well, what do I do on the other days? I have a headache every single day." It doesn't make sense to tell the patient: "Well, you're going to make them more frequent." "Well, I'm already having them every day. How can they get more frequent? And what do I do on the other days? If I take a triptan, I feel perfectly normal, my day is saved, and those days off ..." "Well, take some nonsteroidal anti-inflammatory drugs like ibuprofen." Well, people saying that — the same experts are saying that — if you take too much of ibuprofen, acetaminophen, you still can get so-called medication overuse headache. There's no evidence for that, either. But people will switch from one supposedly rebound-causing drug to a different one. In my experience, I have patients who take triptans every single day and they have normal lives.

Dr. Mauskop (14:40): I should point out this is not my first, second, or third approach to treating patients with chronic migraine. I don't give them, as they walk in, daily triptan. Obviously, you start with preventive therapies, lifestyle changes, exercise, Botox injections, preventive medications. But some days nothing works, that and the only thing that patient finds effective is a triptan. And there is no risk. As we talked about, the long-term risks — after 30 years, we know these drugs are very safe, and there is no reason to withhold these medications. My most popular blog post — and I've been writing this blog for over 15 years — most popular by far is a blog post called, "Daily Use of Triptans." And there are over 300 comments there. People saying, "You saved my life because my doctor says I will die, or have a stroke, or heart attack if I keep taking it. But that's the only drug that allowed me to have a normal life." And many doctors and pharmacists refuse to fill prescriptions for large numbers of these medications. Fortunately, they're not as expensive as they used to be, so cost is no longer an issue, but finding a doctor And during the pandemic I was able to see patients on telemedicine, so, remotely. And people from all over the United States would contact me, make an appointment, and I would prescribe them truly lifesaving medication. So, I can keep going on, on this topic, but

Elizabeth DeStefano (16:09): No, I greatly appreciate you sharing this, because it's certainly fascinating. And vastly different, I'm sure, than what so many of us have heard. And as you highlighted, there can be a tremendous amount of stress and anxiety around this need to ration medications — migraine medications — either because of insurance-related issues, or because of the very deep concern about development of medication overuse headache. So thank you for sharing that.

Dr. Mauskop (16:40): You're right. It's a very important point. I should emphasize what you just mentioned — we call it anticipatory anxiety. People live in this, really, fear and anxiety of not



being able to control it, not having enough medicine. And often people go to the pharmacy, and they give them four pills or nine pills of a triptan. Well, again, I tell patients that's an insurance limit. You can buy extra medicine if you pay out of pocket, and they're not very expensive at all.

Elizabeth DeStefano (17:07): So, one medication to touch on is something that is not back on the market right now. Rofecoxib — a nonsteroidal anti-inflammatory, or NSAID — that had previously been marketed under the brand name Vioxx. How had it been used in migraine? Why was it pulled from the market, and what should we know about the safety of other selective COX-2 inhibitors, or coxibs, in migraine management?

Dr. Mauskop (17:35): Right. We still have one coxib on the market and that's celecoxib. And actually, it's been reformulated in the liquid form specifically for migraine treatment. And rofecoxib, a similar drug that is in trials for migraine patients. And the advantage of those medications over traditional nonsteroidals is that they are less likely to cause stomach problems — bleeding ulcers and such. And the reason the Vioxx (rofecoxib) was pulled off the market was because it was also marketed for people with arthritis. And those people tend to be older and have heart disease. If you are an older person with heart disease and you take Vioxx for a very long time, your risk of heart disease, heart attacks, goes up. Not dramatically, but even a 5% increase is significant enough for people to be concerned. And that was the reason it was pulled off the market.

Elizabeth DeStefano (18:31): In your aforementioned book, you note that migraine attacks can be triggered by deficiencies in nutrients.

Dr. Mauskop (18:39): Yes.

Elizabeth DeStefano (18:40): So I was hoping we could change course a little bit now and talk a little bit about nondrug therapies in migraine management.

Dr. Mauskop (18:47): It's my favorite topic!

Elizabeth DeStefano (18:49): Wonderful, because you mentioned that herbal supplements tend to be safer, you know, than drugs, though there are still safety considerations. So, I was wondering if you could elaborate on that thought about the safety as compared to medications, but also what we do need to keep in mind, still, when using these.

Dr. Mauskop (19:08): Yes, I'm glad you brought it up because — just because it's natural, it doesn't mean it's safe. Botulinum toxin is natural, but if you get poisoning with botulism, you die from that. So that's not necessarily a safe thing to do. And not every herbal supplement is safe, either. So that's why I try to stick with the ones that are proven to be safe. For example, feverfew and Boswellia, and of course the minerals like magnesium has been my area of research — there is very little downside on that; we can talk about, separately, about safety of magnesium. But as far as herbals: butterbur (Petadolex is the brand), is a very effective herb; unlike many other herbal supplements, this one was subjected to a double-blind placebo-controlled trial, which is a very rigorous study.

Dr. Mauskop (20:00): I was one of the three participants — one of the three clinics that participated in this study with 245 patients. So we have good data, solid data showing that 150 mg of this purified form, Petadolex, is better than placebo in preventing migraines. I'm a bit reluctant to prescribe it — and I do prescribe it. But, butterbur, unlike feverfew and Boswellia, is



potentially toxic. So, if you take a raw plant and start making tea out of it, or eating the root of it, could be major trouble. It can cause damage to your liver; it causes malformations in infants and newborns. So that could be a problem. So, if you buy Petadolex, the purified German brand, you are probably safe. And the reason I say "probably" is because Germany actually does not allow the sale of Petadolex, nor does the United Kingdom. So in Europe it's harder to find Petadolex because of this concern. Even though the company has conducted safety trials, the reason the German government decided not to approve it is because the company changed the extraction process.

Dr. Mauskop (21:15): They said it made it even safer and better, but Germany regulates their herbals as strictly as drugs. And they said, "You change the extraction process, you have to repeat all the safety trials." Which is expensive and time consuming. So they didn't do that. We can buy Petadolex, it's fairly expensive — \$50, \$60 a month. But if you go on Amazon, you can find butterbur extract for \$10 a bottle. Then people will say, "Look, why should I pay so much money?" Well, we don't know about the safety of the cheap products. And that's the concern that I have, that people will think that butterbur is butterbur, and they'll switch from the safe one to the much less safe one.

Elizabeth DeStefano (21:55): So, what a perfect example of that while herbal approaches can be such an important part of migraine management, there are still very important safety considerations, particularly, for some to consider.

Dr. Mauskop (22:06): Yes.

Elizabeth DeStefano (22:07): OK. So, the first supplement that you cover in the book we mentioned is magnesium. And you wrote a paper also, titled "Why All Migraine Patients Should Be Treated With Magnesium." So as that title implies, do you recommend that we all take magnesium, and why?

Dr. Mauskop (22:25): So, we published our first paper at SUNY, State University of New York Downstate Medical Center, in 1995 showing that 50% of people during a migraine attack have a deficiency. So half the people could benefit. The reason I said everyone should try it is because you don't know whether you are one of those 50% or not. I don't recommend [it] to all patients in my practice because usually I will do a blood test. And we have to do a special blood test. You have to order "red blood cell magnesium" rather than the most commonly used so-called "serum magnesium," because almost all of your magnesium is hidden inside the cells. So you need to take the red blood cells, open them up, and measure magnesium in those cells, and that's the most sensitive test. So if you do a test, then you know who will benefit, who will not.

Dr. Mauskop (23:16): But for most people — you know, primary care doctors, neurologists, — if you don't order the blood test, it's worth giving everyone a trial oral supplement — magnesium oral supplement. It will not work for 50% of people because oral magnesium is not absorbed in some patients. So you might benefit one out of three of your patients. But it's extremely inexpensive; it's very safe. The only concern is — diarrhea is one of the common side effects, especially if you take magnesium citrate or sulfate. If you take magnesium that's chelated with amino acid, like magnesium glycinate, [it's] less likely to cause diarrhea and you might absorb it. But 10% of our patients don't absorb magnesium even if we know that they are deficient. And those patients come in for monthly infusions of magnesium. So, the major concern with magnesium besides diarrhea is that if you have serious kidney problems — you really would know about it, it cannot be just something you're not aware of — then it can be dangerous to



take too much magnesium. Intravenous magnesium is extremely safe. It's given for eclampsia, a complication of pregnancy, in much larger amounts than what we give.

Elizabeth DeStefano (24:37): You talked about then, obviously, how this relates to possible use in pregnancy. What about in adolescence?

Dr. Mauskop (24:45): That's very similar. Adolescence definitely is when the migraines begin. Now I should tell your audience about symptoms of magnesium deficiency that can help you determine whether you are likely to be deficient or not. You don't have to have them; you can still be deficient, but if you have cold hands and feet, or in general you are [a] cold person. If you have muscle twitching or muscle cramping in your legs or feet at night or anytime throughout the day, that's another symptom. Palpitations is another symptom; brain fog. So magnesium, if you're deficient, it's life-changing. People feel on my ... PMS in women goes away, premenstrual symptoms go away, [you] sleep better, and muscles stop cramping. It really changes your life. But only if you're deficient. If you have enough magnesium, it does nothing at all.

Elizabeth DeStefano (25:36): And if someone doesn't see a change for the better in their migraine after supplementing with magnesium, it may not be that they weren't deficient. It could be that they're not absorbing magnesium through an oral route.

Dr. Mauskop (25:50): That's correct. And the thing to do in that case is to have this RBC magnesium [test]. In the United States it's a standard blood test done by any laboratory. We have two major chains in the United States, LabCorp and Quest. They both do this RBC magnesium test. So it's a standard test. It's not some esoteric test.

Elizabeth DeStefano (26:12): And how can we improve magnesium intake through diet? Is that sufficient?

Dr. Mauskop (26:17): Well, often it's not. Because I have patients who really have a healthy diet. And magnesium by the way, is in the usual suspects, such as whole grains and dark leafy vegetables. And nevertheless, there are people who are not absorbing it, or there are people also who are absorbing it, but their kidneys are excreting it too fast. There are six genetic syndromes of what we call magnesium-wasting nephropathy. So, your kidneys are perfectly fine in every respect except for the fact that they cannot hold on to magnesium, and you just pee it out. So, we've seen those patients, and they get intravenous magnesium and very quickly become deficient again. With time though, if you keep doing it, keep taking it or getting an infusion, kidneys readjust and they have a different set point. So it's not like a lifelong thing that you have to do. That's another interesting element about magnesium.

Elizabeth DeStefano (27:14): One of our Migraine World Summit viewers, named Steve, asked if daily use of preventive natural supplements, like some of those we've been discussing, can cause dependence or be a risk factor for medication overuse headache. Is that something to consider?

Dr. Mauskop (27:31): Well, there were some discussions about feverfew causing this kind of thing. If you take it and then stop, you're going to have withdrawal symptoms, but there's no evidence. And most likely what happens is, if it works for you, and then you stop taking it, it stops working obviously because you're not taking it and your headaches come back. And people often don't remember how bad they were until it comes back. So, the only supplements, including herbals, that you have to be concerned about are the ones with caffeine. And there



are some that do not disclose how much caffeine they contain. So, caffeine is a major, major trigger. And anyone who drinks a lot of coffee knows that if they don't have their cup of coffee in the morning, they'll get a headache. So the first thing we do is limit caffeine intake to maybe one a day — one small cup should not do that. But more than that, we have good, blinded studies showing caffeine withdrawal definitely makes their headaches worse. And again, most people who drink a lot of coffee don't need any studies to prove it to them.

Elizabeth DeStefano (28:36): So, Dr. Mauskop, in your opinion, do you think that safety concerns get in the way of use of treatments, whether that's drug or nondrug therapies that could help people living with migraine?

Dr. Mauskop (28:49): That's absolutely true. And even, we didn't talk about one popular treatment in the United States, and that's chiropractic. I have nothing against chiropractic for back pains, but the neck is a very, very sensitive area, so I would avoid especially what's called adjustments, where the chiropractor twists your neck suddenly. So high-velocity adjustments should be avoided, but gentle work is fine. So yes, even natural treatments — yoga can be ... I like yoga, I do yoga myself. But if you do headstands, shoulder stands, [that] definitely can cause damage to your cervical spine and make your headaches worse, or inversion poses. So use common sense.

Elizabeth DeStefano (29:34): Well, where can we learn more about the work that you're doing and follow your work? You mentioned your blog, maybe you can share that and any other places we can find you.

Dr. Mauskop (29:43): Yes, so nyheadache.com is our website, and nyheadache.com/blog. I usually post on average once a week, all the new developments in the headache field or pain field. And my book you mentioned, it's actually better on Kindle. I have my paper version here too, but the Kindle version, or electronic version, is better because there are a hundred hyperlinks. If you are interested in a particular topic, you just click on that hyperlink and it takes you down a rabbit hole all the way down to various scientific studies and other articles. So even though the book looks slim — but many, many hyperlinks give you thousands more pages of information. So I would go there.

Elizabeth DeStefano (30:32): Well, now I need to get a second version! So, thank you so very much for being here today, Dr. Mauskop, to update us on all of these very important points of safety as relates both to medications and nondrug options in managing migraine.

Dr. Mauskop (30:50): Thank you for having me.