Episode 219: Nutraceuticals for Headache and Migraine | What Works and What Doesn't?

Lindsay Weitzel, PhD:
Hello everyone, and welcome to HeadWise, the videocast and podcast of the National Headache Foundation. I'm Dr. Lindsay Weitzel. I'm the founder of Migraine Nation, and I have a history of chronic and daily migraine that began at the age of four. I'm excited to tell you that we have an esteemed guest with us today who has never been on HeadWise previously. I am here with Dr. Stewart Tepper. Hello, Dr. Tepper, how are you today?

Stewart Tepper, MD:
Hello. It's a great honor to be asked to speak, and I'm happy to do so.

Lindsay Weitzel, PhD:
Thank you for being here. Dr. Tepper is a professor of neurology at the Geisel School of Medicine at Dartmouth, and vice president of the New England Institute for Neurology and Headache. Our topic today is nutraceuticals or supplements and migraine, what works, what doesn't, and what may even be dangerous for us. We are going to ask Dr. Tepper all sorts of questions. He gave a talk on this at AHS, and he just recently published a paper on it. And I can't wait to hear what he has to say. Nutraceuticals are not regulated by the FDA. What sort of guidance or advice do you give patients when they're buying and ingesting supplements or nutraceuticals in general?

Stewart Tepper, MD:
First thing to know, and many younger people are not aware of this, is that nutraceuticals are not regulated by the US federal government or the FDA. There was a special act, the US Dietary Supplement Health and Education Act of 1994, that classifies nutraceuticals as supplements and not medications. FDA does not review them as medications, and there is no U.S. governmental agency that evaluates their effectiveness or the claims that are made for them in terms of how useful they are or their safety. And safety is really only confronted if a major safety issue arises. Actually, if you can buy nutraceuticals made in Canada, the Canadian government does regulate. So you are safer getting them from Canada. There are good websites in the US but be aware of this lack of government oversight.

Lindsay Weitzel, PhD:
That is very interesting. And you're right. I don't think everyone really knows that. I wanted to make sure we started with that information. In the recent paper that you published on nutraceuticals and headache in *Current Pain and Headache Reports*, riboflavin, also known as B2, is the first supplement listed. So, let's start with riboflavin. Does the data show that vitamin B2 is effective in preventing migraine?

Stewart Tepper, MD:
I think overall we have enough studies that we can say pretty clearly that vitamin B2 or riboflavin is effective when taken daily for the prevention of migraine. And interestingly, we know that taking daily riboflavin, usually the dose that's recommended is 400mg per day, which is a big dose, that that is

helpful. But there have been some large studies that looked at dietary vitamin B2. And it turns out that in thousands of patients who were studied, if their dietary B2 was higher, if the amount of riboflavin they took in in their diet was higher, their likelihood of migraine was lower. So, we have kind of two different directions of data that suggest that vitamin B2 is useful in migraine prevention in adults.

Lindsay Weitzel, PhD:
For any of these supplements we talk about today, do we know how long we need to take them before we can expect to see an effect?

Stewart Tepper, MD:
Unfortunately, we do not. The studies on the supplements are relatively small, and unlike the big drug company preventive studies, they didn't have endpoints where they looked at was the drug working at one week or at one month or two months. Almost all of them looked at prevention at three months. I usually just tell patients, as long as you don't have side effects, let's try it for three months daily dose and see whether you notice a decrease in the frequency, severity, or duration of your migraine attacks.

Lindsay Weitzel, PhD:
Speaking of side effects, what are some of the common side effects of supplementing with B2 or riboflavin?

Stewart Tepper, MD:
Riboflavin has very few side effects. I warn patients about bright yellow urine. It will turn your urine bright yellow at a dose of 400mg. Every so often, somebody might get a little bit more gastrointestinal upset from it with diarrhea, but that's very rare. So, most people have no side effects other than having day-glo urine.

Lindsay Weitzel, PhD:
And for the parents that might be watching, can we supplement children, pediatric population that might have migraine with B2? And if so, do we know if it's effective for them?

Stewart Tepper, MD:
I wish we knew. There are two good scientific placebo-controlled trials in pediatrics for riboflavin that were not significant against the placebo. There were two retrospective case series where people just went back and asked their patients and looked at the charts that did suggest a possible benefit. But I think the most judicious thing to say at this point is we don't know if riboflavin works in kids.

Lindsay Weitzel, PhD:
Let's move on to coenzyme Q10. It's been studied in migraine prevention, but we hear about it a little less than some of the other supplements. Is there enough data to show that that is helpful for migraine?

Stewart Tepper, MD:
Again, I think we do have enough data on CoQ10 to suggest that it works taken on a daily basis. I usually recommend a 400mg dose. And what's interesting is that CoQ10 and riboflavin are related in how they probably work in migraine. There are a subset of patients with migraine who don't generate enough energy. And the way that energy is generated in the cells is with a cell organelle called mitochondria.

And when you took high school biology, you probably learned about ATP as a battery that needs to have the phosphate pulled off from the battery in order to generate energy. And it turns out that there's a group of people with migraine who don't generate enough energy, and they don't generate enough ATP. And without going into terribly boring detail, the energy chemical reactions that lead to ATP and to creating the battery for energy may be deficient in some people with migraine. And riboflavin and CoQ10 work in different ways to help stimulate energy for those people that have this mitochondrial problem associated with their migraine.

So they overlap. And what that means is if somebody has a partial response to riboflavin, I usually add CoQ10. And the reverse, if they have response to CoQ10, I'll add riboflavin. And I use the same dose for both, 400mg for both of them, to make it easier. And again, as with riboflavin, the side effects with CoQ10 are minimal. Occasionally somebody will be allergic to it and get a rash. Occasionally somebody will get diarrhea. I can't think of anybody I've ever seen with those side effects. The benefits are pretty obvious. You have B2 and CoQ10. They're both relatively inexpensive. They both have low side effects. They both work along similar mechanistic lines, and you try them for three months and see whether you benefit from them.

Lindsay Weitzel, PhD:
Do we know if CoQ10 is a safe or effective supplement for children with migraine?

Stewart Tepper, MD:
There's one pediatric placebo-controlled trial where it was not any different than having what's called multidisciplinary care, where a child with migraine was given medical care and behavioral treatments and nutritional guidance and so on. And it wasn't any different. But there were a few other studies in which CoQ10 was given to children, and each one seemed to show some benefit for children. There are people who have mitochondrial disorders for whom CoQ10 is used, and that's across all age groups. So, I think the evidence for CoQ10 in kids is a little stronger than for vitamin B2. And whereas there are many more studies for efficacy with riboflavin and CoQ10 in adults. But overall, I'm a little more comfortable with CoQ10 in pediatric age group.

Lindsay Weitzel, PhD:
Let's move on to feverfew. I remember having had migraines since I was a toddler. So many people were telling me to take feverfew because we didn't have a lot of medicines back that. It's been around forever. People used to call it medieval aspirin I remember when I was young. Is it known to be effective in treating migraine? Do we even know?

Stewart Tepper, MD:
I don't think we know. Feverfew is in the chrysanthemum family. It's tanacetum parthenium. And most feverfew in the US is dried leaves of the tanacetum plant. And as a result, because it's being sold as dried leaves, different leaves and different plants have different potency. And the dosage that people are getting and the potency of what they're getting is not known, is not anyway the same from lot-to-lot.

The other thing about feverfew is that it does have a lot of effects. The plant has a lot of effects. Some of these effects on the body are probably good. Some of the effects are unknown. Some of the effects might be bad. So, you have a pretty complicated situation where you have a dried plant with different potency and lots and lots of effects. And there have been quite a few, between 6 and 10, studies on feverfew that have been evaluated over and over again by different groups using scientific methods.

And each of these reviews that have been done over decades, where they take all the reviews, all the studies on feverfew and then systematically grade them, come to the same conclusions. The studies are all over the place. They're variable. They're hard to interpret. And what all these reviews end up saying is no firm conclusion can currently be drawn about whether feverfew works preventively. And inconsistent findings could be due to all sorts of reasons, because the dried leaves are so different in dosages and extracts, and some of the studies weren't very good. And you add that to the fact that it has all of these effects. And then to some side effects, it can cause, the actual plant, the ingestion of feverfew can cause widespread inflammation of the oral mucosa and tongue, that is the mouth, dermatitis. And also, there was one British study that reported that when people stopped it, they got all joint aches, what are called arthralgias, and they also had mouth ulcers that were described.

And so, my own feeling about it is that we don't know whether it's really effective. We don't have really clear safety studies. And the differences in doses and characteristics of the dried leaf preparations and then so many cellular effects suggest caution in recommending it for use. And I don't generally recommend it for my patients.

Lindsay Weitzel, PhD:
That's really good to know because we hear about it all the time. I'm glad that I asked that question. Let's move on to something that I think we've all heard about probably the most. Let's talk about magnesium. It seems like the supplement we hear about constantly in the setting of migraine. Do we have data to show that it’s effective in migraine prevention?

Stewart Tepper, MD:
Yeah, I think we have reasonably good data on magnesium. And again, as with riboflavin, dietary magnesium seems to be associated with less migraine. And in addition, we have studies on magnesium. And we have lots of reasons to think that magnesium can work. There are a variety of effects of magnesium in the brain that could be very helpful in terms of migraine. Especially, magnesium has been thought to be helpful in migraine with aura and in menstrually related migraine. Those are two groups where we use magnesium a lot.

I was at a meeting over the weekend with Todd Schwedt, who's the president of the American Headache Society, and we were comparing notes. And he and I both use magnesium, recommend

magnesium very, very frequently. Almost to every patient who has migraine with aura, I recommend it. There are large numbers of studies on magnesium that make us confident about its effectiveness.

Now there are different kinds of magnesium. For example, magnesium citrate is used for constipation. It works as a laxative. So, you probably wouldn't want to take magnesium citrate. And some of the reviews really can't tell you which the best form is or what the best doses. Some do make recommendations, but I think the ones that are most frequently used in the U.S. would be magnesium oxide, magnesium taurate, magnesium glycinate. And I generally recommended a dose of 500mg daily.

And what stops us with magnesium in terms of patients use is if a person gets gastrointestinal upset because it can cause diarrhea. And once a person gets diarrhea from magnesium, it's pretty hard to find a magnesium dose that doesn't cause gastrointestinal upset. On the other hand, a lot of our drugs are constipating, so adding magnesium in the setting of drugs that are constipating can be helpful for people. And as I say, I use an awful lot of magnesium supplementation, or I recommend it in a lot of patients.

Lindsay Weitzel, PhD:
What about IV magnesium? Maybe not all over the country, but I know where I live there's a lot of vitamin bars, etc. and you can get IV magnesium, which I know some people with migraines will do. Is this good for the acute treatment of migraine?

Stewart Tepper, MD:
Yes. There are a number of studies, placebo-controlled trials as well as case series, that show IV magnesium can terminate attacks of migraine, especially in people that have aura. So yes, if you were in the throes of a migraine and your practitioner could provide you with IV magnesium, that's not a bad thing to do. And we often will add magnesium in our infusion suite in somebody who's having a prolonged migraine.

Lindsay Weitzel, PhD:
Let's move on to melatonin. Most people think melatonin is just used to help us fall asleep, but it often is mentioned in the setting of migraine. Is there actually evidence for the use of melatonin to prevent migraine or any other type of headache?

Stewart Tepper, MD:
There are some studies on it. They're not very good. They're pretty small. It's really hard to interpret and I don't generally recommend it for prevention of migraine. The Canadian Headache Society published their recommendations, their guidelines, in the summer of 2024. And they said you might consider melatonin in somebody who has a sleep disorder. But again, they thought the quality of the evidence was quite weak. It's also been described as helpful in cluster headache. I think the quality of the evidence there is also quite weak.

There's one rare group of headache disorders that are called trigeminal autonomic cephalalgias or TACs. And these rare headache disorders, there's two types of TACs that respond only to one a non-steroidal anti-inflammatory called indomethacin. And many people can't take indomethacin. It has a

long list of potential side effects. Melatonin is structurally related to indomethacin. And so sometimes we'll use melatonin to reduce the amount of indomethacin that somebody has to take, or in place of indomethacin. Sometimes you get lucky.

But our use of melatonin is pretty low. And one of the reasons why it's particularly low in the United States is that remember I said at the beginning that the federal government doesn't evaluate what's really in the product that you're buying as a supplement or a nutraceutical. And in the case of melatonin, there was a study that looked at 31 different types of melatonin that were for sale around the country. And it was pretty shocking because even with the same brand, from a bottle to another bottle of melatonin, the amount of melatonin within the product could vary by as much as, wait a second I'll tell you, 465%. That's how much lot-to-lot variability there was.

And it didn't meet the label within 10% in almost three quarters of the bottles that were tested. So, melatonin that's sold in the United States is likely to be impure. They found other substances that were identified in the supplements of melatonin. Again, if you're going to take melatonin, you probably should get it from Canada.

But there are several generic melatonin receptor agonists that are FDA approved and that are available. And so if you want to use a melatonin like drug for sleep or see if it works for migraine, one of these melatonin receptor agonists can be used. One of them is called ramelteon. And there are other generic melatonin receptor agonists that are also available.

And that's what I've been telling patients. I tell them the melatonin that is available over the counter in the US is not so good, probably impure. We can either get it from Canada or we can try one of the melatonin receptor agonists.

Lindsay Weitzel, PhD:
Now that you've mentioned that I have a broad question about the supplements we've mentioned so far. Is there any concern when you're talking to patients who might already be on a number of preventive medicines for migraine about also adding supplements? Is there any health risk, liver etc.? Is that something that people should be worried about?

Stewart Tepper, MD:
Of the ones that we have mentioned, for the most part, no. Because if there's a big safety issue, then the FDA can get involved. And I do add supplements to preventive agents for migraine, but I warn patients. And at my office we actually did some research on quality of supplements, and we do make recommendations to patients about particular brands or websites that we think might be more likely to be high quality.

Lindsay Weitzel, PhD:
We're going to move on to another one, another supplement. I was going to ask you about butterbur. It's also called petasites. We hear a lot about this one. This is another one that's been around since I was a kid. People were telling me to take it when I was younger. What kind of evidence do we have for efficacy and safety of butterbur for the prevention of migraine?

Stewart Tepper, MD:
Petasites works for migraine prevention. I think everybody agrees. Good randomized controlled trials on petasites and butterbur showed that it is effective in migraine prevention. The controversy about butterbur and petasites is that there is a toxic set of chemicals that can occur in the plant called pyrrolizidine alkaloids, which for the sake of discussion, we'll just call PAs.

And the PAs are supposed to be extracted from the butterbur plant in order to actually market butterbur for migraine prevention, let's say. The debate is how well do they get the PAs out of the butterbur plant. Because we know the butterbur works, but the issue of the PAs is pretty significant. In a lot of the world, the butterbur, petasites supplements are not available. They were taken off the market. For example, in the UK in 2012, they have a Medicines and Healthcare Products Regulatory Agency, the MHRA. They pulled all the petasites products from the UK market. Many of them have been removed in other European markets. And the two that are supposed to be PA free, one of them is sold in the US called Petadolex.

And I think the best source for what to say and what to do about petasites is from the NIH, the National Institute of Health website for the US National Center for Complementary and Integrative Health. [https://www.nccih.nih.gov] This is the governmental site for the US. And with your permission, I'm going to read a couple of paragraphs of what the NIH website says about petasites preparations.

Several studies. I will just start quoting.

Several studies, including a few studies of children and adolescents, have reported that PA-free butterbur products seem to be safe when taken by mouth in recommended doses for up to 16 weeks. However, some products claiming to PA-free may not in fact be. For example, Petadolex is marketed as a PA-free butterbur product, but it has been associated with liver damage in some people, suggesting that it may have had PAs. Also, the safety of longer-term use of butterbur has not been established.

Other adverse events include belching, headache, itchy eyes, diarrhea, breathing difficulties, fatigue, upset stomach, drowsiness, and allergic reactions.

Butterbur products with PAs should not be used during pregnancy or while breastfeeding, because they may cause birth defects or liver damage. Little is known about whether it's safe to use PA free butterbur during pregnancy or while breastfeeding.

If you're planning to use butterbur or to give it to your child, tell your or the child's healthcare provider. Healthcare providers may consider liver function monitoring for people using butterbur.

Those are the recommendations from the NIH website. And that's what I share with patients.

Lindsay Weitzel, PhD:
That's very informative. If you are taking it, perhaps tell your healthcare provider and perhaps be monitored. But there is some evidence that it could be efficacious in the treatment of migraine. So that one is a very interesting one, so we spent some time talking about it.

Before we close, are there any other supplements that you think we should cover or possibly supplements that are thought to be effective for migraine that people take that maybe we should discuss because they aren't known to be effective. Anything like that that we need to cover?

Stewart Tepper, MD:
Well, every day I hear about a new supplement and yes there's a lot. The data are not as usable. Cannabinoids, the derivatives of marijuana, were not covered in my article. And there are some cannabinoid products that are available without prescription and CBD products in particular. And one of the issues about CBD is it doesn't seem to penetrate the brain very well. So, it's kinda hard for me to see that CBD, which is available over the counter, is going to be likely very helpful for migraine. There was one prospective study on using different inhaled formulations of cannabinoids with different mixtures of THC and CBD. And the only ones that seem to work to terminate migraine were those that contained THC. So again, with cannabinoids, we don't know how much THC is really in it. We don't know how much CBD is really in it. It's very difficult to advise patients about what to do with respect to marijuana derivatives. But that is a whole other kettle of fish.

Lindsay Weitzel, PhD:
Yes, that is a whole different podcast in and of itself. Thank you so much for being here. This was very informative. I hope everyone got something out of this podcast. And thank you to everyone for joining us. And please join us on our next episode of HeadWise. Bye bye.

Stewart Tepper, MD:
Thank you very much.