MIGRAINE WORLD SUMMIT

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# TRANSCRIPT

## PSYCHEDELICS FOR THE TREATMENT OF HEADACHE DISORDERS

**EMMANUELLE SCHINDLER, MD, PhD**
**ASSISTANT PROFESSOR OF NEUROLOGY**
**YALE SCHOOL OF MEDICINE**

**Introduction** (00:05): It shouldn't be a surprise that these substances would have effects in headache disorders, as they are chemically and pharmacologically very similar to existing headache medications. But one of the key points is the way that they're different is this long-lasting effect after limited dosing. There's nothing else out there in headache medicine that can do that. Even the monthly injections of the CGRP-targeting antibodies, it's once a month, but the drug stays in your body the whole time. With psilocybin and LSD, the drug is metabolized — it's out of your body by the next day, essentially, but it's still having an effect. So that is what makes these drugs so exciting in headache; it's a completely different method of treatment.

**Paula K. Dumas** (00:49): Decades ago, one of the hottest areas of therapeutic research being investigated by leading universities around the globe was suddenly shut down despite showing great promise. Now it's back again, with the potential to help ease the pain of many conditions that have become an epidemic: depression, anxiety, insomnia, headache, PTSD, and many more. Our next guest gave a keynote lecture on her groundbreaking research into this topic at the American Headache Society Conference in 2022. If other treatments have failed you, or you deal with cluster migraine or post-traumatic headache, don't miss this talk. Dr. Emmanuelle Schindler is the medical director of the Headache Center of Excellence at VA Connecticut Healthcare System and assistant professor of neurology at the Yale School of Medicine. She's also an award-winning researcher in the field of headache medicine and psychedelics. Dr. Schindler, welcome to the Migraine World Summit.

**Dr. Schindler** (01:48): Thank you, Paula. I'm very happy to be here.

**Paula K. Dumas** (01:51): Well, this is a really important topic and there's a lot to cover today, so we're going to dive right into it. Start us off by telling us: What exactly are psychedelics?

**Dr. Schindler** (02:00): Great question. And that's usually how I start off when I talk about psychedelics. So, psychedelics are drugs that bind to, and activate, serotonin 2A receptors, and that have well-known psychotropic effects that are called "psychedelic effects." There are some other compounds that sometimes get lumped into the category of psychedelics, such as ketamine, for instance, but ketamine doesn't bind serotonin 2A receptors. It's an antagonist at the NMDA receptor. So it has a different pharmacology — some overlapping psychotropic effects but it is very different. MDMA, also known as ecstasy, often gets lumped into the psychedelic group, but its main pharmacologic action is that of increasing serotonin at the synaptic cleft. So, again, a different pharmacology and a different psychotropic effect with some overlap with psychedelics, but it is different. So when I talk about psychedelics, I mean the serotonin 2A agonists.

**Paula K. Dumas** (03:10): Well, I think when most of us hear the term psychedelics, we think of the '60s, we think of LSD, some people might even think of mushrooms. Can you talk a little bit about LSD and microdosing? What is that?

**Dr. Schindler** (03:24): Sure. First off, the term microdosing, to me, is not very clear. You have to specify what you mean when you say "microdosing." In general, it means taking a very small dose of a psychedelic — whether it's LSD or whether it's psilocybin — but how low that is, again, not specified by the term microdosing. And then how often is not specified. You can take a low dose once in your lifetime and be done with it, or you can take a low dose every day forever and call it microdosing as well. So, those are very different methods of treatment. And so, it has to be specified. And there are people who are experimenting with microdosing in the way of taking frequent doses over the long term, but this is sort of a new area; this is not how psychedelics



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have been used for the past thousands of years. So, this area will have to be studied very carefully.

**Paula K. Dumas** (04:26): How about psilocybin and mushrooms? This is a topic I've heard discussed, particularly in the cluster community, but you've been doing some research in this space. Can you talk about that?

**Dr. Schindler** (04:36): Sure. Cluster headache, as you know, is a very debilitating headache disorder. And there are some approved treatments, but they're very few and not always accessible. And cluster headache patients will often try anything and everything to treat their headache disorder. And it was in the late '90s when a Scottish cluster headache patient accidentally found out that when he took LSD, his normal cycle was not happening. So, he shared this information online in the early days of the internet, and the information spread, and other patients started trying it and finding that there's a long-lasting effect after taking just a couple doses, or even one dose of a psychedelic, whether it's LSD or magic mushrooms. It's somewhat easier to get magic mushrooms than LSD. And so, cluster headache patients have migrated in that direction to talking mostly about psilocybin mushrooms, or magic mushrooms. But this finding was accidental. Just like the great discoveries — like penicillin — were accidental, it has now spread, and patients the past 20 plus years have been using psychedelic mushrooms and also other psychedelics to manage their condition.

**Paula K. Dumas** (06:05): And one other psychedelic that we'll touch upon briefly is mescaline, or some people know it as peyote, right? Which I associate with Native American communities. Is that right?

**Dr. Schindler** (06:17): Correct. Yes. And I don't hear as much ... of patients saying that they use mescaline for their cluster headache, but I have heard one or two cases. It's not as easy to obtain, and if I'm correct, the peyote cactus — there are fewer and fewer cacti, and so perhaps harder to get as well.

**Paula K. Dumas** (06:39): Now, some people who are watching this may have heard a little bit about this field after Michael Pollan's 2018 book, or the 2022 Netflix miniseries that was called, *How to Change Your Mind*, which is focused more on mental health. But what effect did Pollan's work have on the research community?

**Dr. Schindler** (06:59): Yes. I was getting a lot of emails when Michael Pollan's book came out and the Netflix documentary, as well. While those productions were focused more on mental health, there may have been mention of pain and headache, or they may have looked online and seen that there is some work in headache, as well. So, it's certainly brought attention to the field, and taking a look at psychedelics as medicines, whether it's for mental health or for pain and headache. So, that really got people interested. And I think funding agencies as well, which in the research world is important.

**Paula K. Dumas** (07:35): Definitely is. So, let's talk a little bit about the therapeutic potential of these drugs, because people want to know: Do they work? Generally speaking, for which conditions do these psychedelics seem to show promise?

**Dr. Schindler** (07:48): Well, much of the research, and the more advanced phase 2 studies, are in mental health, so psilocybin and depression. And, very recently, psilocybin in patients who have alcohol use disorder has been shown to be effective. In terms of headache disorders,



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there's less research. There are decades of anecdotal research from cluster headache patients and some migraine patients, as well. But the controlled studies are just getting started. So, there's a pilot study that I did in patients with migraine that was published last year. It only had 10 patients, however, and then I also finished the study that's in cluster headache, it had 14 patients. So, in these small studies there is promise supporting further research, but it's not really sufficient to say that this is going to be something that will, first off, work for everybody, be safe in everybody, and we still have to figure out dosing, and the regimen. And there's still a long way to go, but I believe that there is promise in various headache disorders.

**Paula K. Dumas** (09:05): Yeah. So, a number of people in our community have been asking about this — Laura, Shari, and Wheatie — they're all eager to learn about the latest research on the effectiveness of psilocybin, in particular on migraine and cluster headache. And you mentioned that the studies that you've done are really small, but what does it show so far?

**Dr. Schindler** (09:25): Sure. So, for the migraine study that, again, had 10 patients ... it was a crossover study. So, each patient got both a placebo and then they got psilocybin. And the dose of psilocybin was about 10 mg, which is a relatively low dose. As a comparison, the studies in mental health used 25 or 30 mg; so less than half of the doses used in mental health. And then we had patients keep a headache diary for two weeks after each dose. So, only looked at the effects over two weeks. But in those two weeks after dosing, there was a 50% reduction in the number of migraine days after psilocybin, and not much changed after the placebo. And the pain intensity of the migraines that did happen was also reduced by about 30%. And going along with that, patients used fewer triptans and over-the-counter medications for the acute treatment, and they could function better during migraines. So, the migraines were less frequent and less severe when they happened in that two-week period.

**Paula K. Dumas** (10:40): Yeah. And that's a very small study for a very short time. So it is promising, which just says we need more research and more money to do this. As I'm understanding it, this was used as a preventive, right? Not to manage an attack, like an acute medication?

**Dr. Schindler** (10:57): Correct. Yeah.

**Paula K. Dumas** (10:58): OK. And did it have any effect, or did you measure whether it had an effect on the comorbid conditions that people with migraine often experience, like mood and sleep disorders?

**Dr. Schindler** (11:08): So, I had a quality-of-life scale that involved anxiety and days with a poor mood; not a standardized screen for anxiety or depression. But people started out with a relatively good mood and low anxiety, so I wasn't really able to see a change. But just when I followed up with patients in this study, a lot of them said that they felt less anxious, particularly less anxious about their migraine disease — about the fact that they might get a migraine. They weren't as worried about it. I found the same reports with the cluster headache patients. They were less worried about their disease and their next attack, but that's sort of anecdotal. There wasn't a measure for that, but I want to measure it in future studies.

**Paula K. Dumas** (11:58): So, I know that you don't consider yourself an expert in mental health studies, but you've had some exposure to them. And because these often travel together in people with migraine — and we deal with stress, anxiety, depression, and insomnia — if



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something like microdosing effectively reduced all those triggers in people with migraine, could it effectively, or theoretically, keep us below our migraine or cluster threshold?

**Dr. Schindler** (12:29): So, I don't plan on studying microdosing (the idea of taking low, very low doses frequently) for a couple reasons. One is, that's not any different than taking an antidepressant every day. You take something every day, and over time — some work faster, some take more time — you have a reduction in those symptoms. And also, as I mentioned before, the way that psychedelics have been used for thousands of years involves moderate to high doses infrequently. And we know that that's safe and that's not habit forming, and it doesn't cause organ damage. But we don't have decades and centuries and millennia of experience with the frequent use of these drugs. And so, if at any point microdosing, with the definition of taking small doses chronically, comes to be, I'd want to see a lot of safety data first.

**Dr. Schindler** (13:33): So, safety and the fact that that dosing regimen is not much different from taking an antidepressant. The way that psychedelics are studied in mental health is — similarly to what I was doing — is a single dose and then a long-term effect. So, you could argue the same thing that microdosing for mental health is no different from taking antidepressants. What makes psychedelics remarkable is that you don't need to take them every day; that you can take a low-ish to moderate dose and have weeks or months, or in mental health studies over a year, of therapeutic benefit. So, if anything, the single dose that I used in the migraine studies might have had an effect on the mental health.

**Dr. Schindler** (14:21): There's no need for the microdosing with the small doses every day. But it's kind of a chicken-or-egg thing. Where, is it that the headaches are getting better and so you're feeling less anxious and depressed? Or, is it treating the anxiety and depression and therefore helping reduce the headache burden? So, there's a little bit of chicken or egg there. But I will say that in the studies with psychedelics in mental health, they don't just give the drug and that's it. They do extensive psychotherapy for weeks: prior to the dosing session; during the dosing session, it's very intensive, it's higher doses, so there are people monitoring; and then afterward they continue the psychotherapy. And so, in mental health, it's actually psychedelic-assisted therapy. So it's like adjunct therapy. They're already doing psychotherapy for their alcohol use or their depression or anxiety, and then they use psychedelics. Sometimes a single dose, sometimes they have two sessions a week or two apart. So sometimes they will study ... they'll look at more than one dose. So, whether giving the drug without all that extra support can help the anxiety and depression in patients who have migraine would have to be studied, but there might be an effect. And I anecdotally noticed that patients were less anxious. So it is possible that using a psychedelic for headache management may also, in turn, help the mental health side of things.

**Paula K. Dumas** (15:55): Good. Well let's underscore, we're at the very early stages. And I do want to dive into the risks in just a second. But first, I wanted to ask you about veterans, because you work closely with the U.S. Veterans Administration. What potential do you think these medications have for military vets with post-traumatic headache?

**Dr. Schindler** (16:16): Yes. So, I have been working at the West Haven V.A. for, if you count my training, 10 years now. So, I'm very familiar with the veteran population and their needs and the complexity of their headache disorders. And I do have a small study running right now looking at psilocybin in patients who have post-traumatic headache. And it's still running, so I can't speak about results yet. I'm still blinded too, so I can't speak about results yet. But I'm hoping that not only will it help the headache, but all the other post-concussive symptoms that come with it:



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insomnia, vertigo, double vision, concentration problems, and some of the mood symptoms, as well. But because it's a complex condition it may involve more than just giving the medication. It may have to be more of an adjunct with supportive therapy.

**Paula K. Dumas** (17:24): All the hype that's coming up these days with Pollan and Netflix and others, we have to talk about risks. What are the major categories of risk that you see?

**Dr. Schindler** (17:33): Yes. This topic must be discussed when talking about psychedelics. And there are a number of risks. First off, any medication has risks. There are some people who shouldn't take Tylenol, even, or shouldn't take Motrin. Similarly, there are some patients who should never take a psychedelic, and these would be people who have, for instance, a psychotic condition that's poorly controlled. And if you're not in a study specifically studying the effects of psychedelics in patients who have psychosis, it would be very risky to take a psychedelic. In patients who have manic disorders, too, psychedelics can prompt a manic episode, as well. So those are some examples, and patients who have cardiac disease or who've had a stroke in the past that also places them at higher risk because psychedelics — similarly to the triptans, which are also contraindicated in patients with a stroke or heart attack history — similarly, they constrict blood vessels, they're very activating to the cardiovascular system, and so those patients are at higher risk. So there are some people who should never take it, or perhaps, only if it's being studied in that population specifically.

**Dr. Schindler** (19:01): In people who don't have those conditions, I'm sure you've heard of a "bad trip." Everybody has the potential for a bad trip. I mean, any psychoactive agent — for instance, if you're drinking alcohol, if you start off in a bad mood and you drink the alcohol, you may just be in a much worse mood. So the same thing can happen with psychedelics; it can amplify whatever you're currently feeling. And so, you have to be careful in terms of when you're taking it, and what state you are in.

**Dr. Schindler** (19:34): Also, because psychedelics alter your sensation, your perception, and your consciousness — this is where, back in the day when psychedelics were being stigmatized because they were so dangerous — there were cases of people jumping out of windows, kids coming across their parents' stash. But these are not direct examples of the drug causing morbidity and mortality. If your thoughts are messed up, then you may think you can fly, so you jump out of a window. And then the examples that were brought up in terms of kids coming across their parents' stash and then sometimes overdosing. First off, it's very hard to overdose on these drugs because if you're using mushrooms; the mushrooms themselves, you have to ingest more mushrooms than your body would ever accept, to overdose. With LSD, because it typically comes on papers or as a powder, you could take a very, very high dose and have trouble. And that's what has happened in the past where people accidentally, maybe took much higher doses than would ever normally be used.

**Dr. Schindler** (20:51): But overall, the toxic dose of these drugs is nowhere near the recreational or the therapeutic dose. But that's when considering a single dose, and that's what brings me back to the whole microdosing thing. Taking one high dose, once a year is fine. Taking small doses every day? What does that do to your kidney, to your liver, to your other tissues? There's a lesson to learn from headache medicine, actually. So there was a drug that was actually developed off of the LSD molecule called methysergide, and it was a headache preventive for migraine and for cluster for many years. It was taken off the market because it caused fibrosis of certain tissues, including your heart valves.



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**Dr. Schindler** (21:40): So, LSD is chemically very, very similar to methysergide. And so, it's a big difference too, from taking methysergide once versus taking it every day. People saw the difference when taking it every day but there could be problems. So, the dose and the regimen that you're using must be considered. And I feel like the chronic-dosing regimens have not been studied for safety, systematically. And so, I would caution patients about trying to experiment with that, or focusing only on that. Plus, like I mentioned, taking something every day for headache — I mean, that's what you do when you take topiramate every day or take amitriptyline every day. It's the same thing. That's not really a novel mechanism. The novelty with these drugs is the single dose, or very few doses (two or three) and the long-lasting effects — weeks, months, and in the case of some mental health studies, over a year. So that's what makes these so interesting, but we can't forget about the safety.

**Paula K. Dumas** (22:50): Right. So, I'd like to talk a little bit about some questions that we've gotten from our community and about the access to these medications, because people are really curious. Kim said: If I have to travel for it, I'm open. As I believe this research and the anecdotal documentation are sufficient, and I feel safer trying this than I would some of the rush-to-market pharmaceutical medications. So how and where might Kim and others join a clinical trial?

**Dr. Schindler** (23:20): So, all the clinical trials that are going on in the U.S., and also in different countries, will be listed on clinicaltrials.gov. So, we can go on clinicaltrials.gov and search migraine, or cluster, or post-traumatic headache, and then there's an option for another term. Then you could put psilocybin, and you can search for the studies that are actively recruiting. And yes, some you will have to travel; there may be some that are local. I am working for some next-level studies, which will be multi-site so that patients may not have to travel so far. But yes, they'll all be listed on that site.

**Paula K. Dumas** (24:02): Because you're based in Connecticut, where else is this type of research being done in the world?

**Dr. Schindler** (24:09): So, migraine, there's none right now, aside from what I'm doing. There is a SUNCT [short-lasting unilateral neuralgiform headache with conjunctival injection and tearing] study that's out of London. There is an LSD cluster headache study that's happening in Switzerland — you have to be fluent in German to take part in that study. And there's a cluster headache study that just finished in Denmark. And then there's my post-traumatic headache study that I'm doing. So, in the U.S., there's no other place where it's happening. But hopefully, people will be interested and may want to, you know ... especially out on the West Coast. Also, we have had patients from the West Coast travel to take part in my studies. But yes, it's a very few places right now.

**Paula K. Dumas** (25:13): I do want to ask you to try to compare this whole class of psychedelic drugs to the other things that we are familiar with. So, for example, plant-based supplements like butterbur or feverfew. Well, let's start there.

**Dr. Schindler** (25:29): Sure. So, the butterbur and the feverfew have to be taken every day. So again, it's a supplement that can change the functioning of cells and reduce inflammation. Those are some of the thoughts behind how they work, but they have to be taken every day. So, it's



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very different from the concept, again, of taking something once or twice and then being done for several months.

**Paula K. Dumas** (25:54): Right. How would you compare it to CBD or cannabis?

**Dr. Schindler** (25:58): I don't have a ton of experience with those substances, but in general, what some research and what patients often tell me — especially cluster headache patients — is that cannabis helps with some of the associated symptoms of their headache disorder: the insomnia, the anxiety. Or it can also dissociate them from their headache pain. So, the pain is still there; they just don't notice it, and that's all helpful. But there's very little controlled research with cannabis in headache disorders. So it's hard to have a comparison, but, in general, I feel like psychedelics may more directly affect the headache disorder itself, versus some of the ancillary symptoms.

**Paula K. Dumas** (26:47): That makes sense. Ketamine nasal sprays or infusions have also been getting a lot of buzz. How are psychedelic drugs alike or different from ketamine?

**Dr. Schindler** (26:58): Ketamine is a little bit closer in terms of how it can be used, because ketamine can also be given as a short course, and then that can give a long-lasting effect. And that's similar to how psychedelics would work. Ketamine can also be used as an abortive and especially in patients of cluster headache. But that wouldn't be very practical to take a psychedelic every time you had a headache. And so, ketamine may be a little bit more flexible in terms of how it's used. But I don't believe it has as long-lasting of an effect as the classic psychedelics do.

**Paula K. Dumas** (27:37): Great. And you gave us some good examples of how these psychedelics are similar to some of the pharmaceutical medications that we're familiar with. Anything else you wanted to add there?

**Dr. Schindler** (27:50): I think, well, yes, I gave the example with the LSD and the methysergide, and psilocybin is very chemically similar to the triptans. So I guess one message from that is that: It shouldn't be a surprise that these substances would have effects in headache disorders, as they are chemically and pharmacologically very similar to existing headache medications. But one of the key points is that the way that they're different is this long-lasting effect after limited dosing. There's nothing else out there in headache medicine that can do that. Even the monthly injections of the CGRP-targeting antibodies, it's once a month, but the drug stays in your body the whole time. With psilocybin and LSD, the drug is metabolized — it's out of your body by the next day, essentially, but it's still having an effect. So that is what makes these drugs so exciting in headache; It's a completely different method of treatment. And so, as we know, we need many more treatments for the different headache disorders, and so this is a truly new tool in the toolbox.

**Paula K. Dumas** (29:02): Well, that's very exciting unto itself because there are people who don't respond to some of the medications that have come out recently — as fantastic as they are, they're not as responsive. And so, having another option that's in the pipeline and being researched gives a lot of people hope that there may be something for them in the future. So, any final thoughts you'd like to leave with the audience?

**Dr. Schindler** (29:25): I would like to underscore again: the safety with these compounds. I do harp on it a little bit, but it's just because we just had a couple decades of no research, and



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those of us doing research in the area now, we're very grateful and extremely careful with our research. We don't want something bad to happen to put them back in the box. So, while exciting, there are going to be safety issues and the research in headache disorders is still very preliminary, but very promising. So I am excited, but I am also cautiously optimistic in terms of — emphasizing cautiously — how these drugs will become medications eventually.

**Paula K. Dumas** (30:15): That's right. Well, caution is a good idea in this case. And I would like to just reiterate that anybody who's interested in a clinical trial can go to the clinicaltrials.gov in the U.S.; and the other organizations in other countries that may be doing some of this research and look for organizations, nonprofits, that are helping to fund some of the research so that we can continue to explore this area that you're doing. So, Dr. Schindler, thank you so much for being a part of the Migraine World Summit and sharing the insights from your research this year.

**Dr. Schindler** (30:51): Sure. Thank you very much.



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