SOMETHING FOR THE PAIN

EPISODE 27: Surveying Substance Use Disorder: Psilocybin

(50 mins)

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[cue guitar music]

[Sam Steffen]

This is *Something for the Pain*, a podcast produced by Project ECHO Idaho, made for Idaho's healthcare professionals working to prevent, treat, and facilitate recovery from opioid and substance use disorders throughout the Gem State. I'm your host, Sam Steffen.

[theme song]

Today we're continuing our theme of 'Surveying Substance Use Disorders' and are going to be talking about Marijuana. This episode features a presentation by Dr. Natalie Gukasyan, Psychiatrist and Medical Director at Johns Hopkins University Center for Psychedelic and Consciousness Research in Baltimore Maryland , titled "Psychedelic-Assisted Therapy: Overview of Treatment Model and Current Evidence for Efficacy." This lecture was recorded on June 2, 2021 as a part of ECHO Idaho's Behavioral Health in Primary Care series. Here to introduce today's presenter is ECHO Idaho's former Director, Lachelle Smith.

[Lachelle Smith]

Welcome to ECHO Idaho Behavioral Health in Primary Care. I'm Lachelle Smith and will facilitate the conversation today. We are so over-the-moon pleased to have Dr. Gukasyan with us from Johns Hopkins Center for Psychedelics and Consciousness Research who will be giving the talk on "Psychedelic Assisted Therapy: Overview of Treatment and Current Evidence for Efficacy" today. And Dr. Gukasyan, if you want to introduce yourself, and the floor is yours!

[Natalie Gukasyan]

Sure. So, hi! My name is Dr. Natalie Gukasyan, I'm a psychiatrist and a post-doctoral fellow over at the Johns Hopkins Center for Psychedelic and Consciousness Research, and I'm excited today to be here with you and share a little bit about what's going on in the wild world of psychedelic assisted therapy research and sort of give you guys an overview of what's happened so far, where we're at now, what the future kind of looks like. This will be a pretty broad talk. I tried to tailor this to providers, primarily primary care providers and some behavioral health specialists, so I tried to keep it friendly for that sort of audience.

So here are my disclosures: so I'm a co-investigator on a multi-site clinical trail of psilocybin for major depressive disorder, it's funded by the non-profit Usona Institute and I'm a co-investigator on a pilot study of psilocybin for anorexia nervosa which received philanthropic funding from a number of sources

including Tim Ferriss, Matt Mullenweg, Craig Nerenberg, Blake Mycoskie and the Steven and Alexandra Cohen Foundation.

And here are our basic sort of learning objectives for today. So first we'll talk a little bit about the basic mechanisms of classic psychedelics, the two general kinds of explanations that we have for how these work, what we do and don't know; and next we'll move onto just an overview of what the treatment actually looks like, meaning like what happens in the session rooms and before and after and who's there and what we understand about what is optimal for now; and finally we'll go through just briefly sort of the level of evidence for efficacy in major depressive disorder which is the indication for which psychedelic treatment is furthest along, and just a little bit about some other conditions that this is being studied for.

So before we really get into it, it would probably be helpful to sort of agree on what we are talking about here because there's a number of different terms that are used to talk about these substances. So right now 'psychedelic' is the predominating term that's used and we'll focus on classic psychedelics, in particular psilocybin. So the term 'psychedelic' was coined by Humphry Osmond who was a Canadian psychiatrist and he worked with LSD back in the 1950s. And they first found this term in a letter that he wrote to Aldous Huxley in which he wrote, quote, "to fathom hell or soar angelic / just take a pinch of psychedelic." And so it comes from the Greek roots "psyche" and "delos" meaning "mind-manifesting." The term "hallucinogen" is still pretty widely-used especially in medical spheres, but has some weaknesses, in particular that it doesn't really convey the full spectrum of drug-effects that we see with psychedelics, and in particular it doesn't really capture the types of effects that we think are associated with therapeutic efficacy. And another term you might see now and then is "entheogen" which, "entheos" the root, translates to "being full of god" or "inspired" or "possessed." And that term can be used to describe drugs that cause one to experience feelings of inspiration, often in a religious or a spiritual manner. The other weakness with "hallucinogenic" I think is that it usually refers to a class of drugs that's a little bit broader than what we're talking about today, which I'll get into in just a second. But what binds this class of drugs is that they are all agonists or partial-agonists at the serotonin 2A or 5HT2A receptor. And in terms of their subject of effects, they produce acute and pretty profound changes in mood and perception and cognition and in many cases these effects are accompanied by a sense of deep personal meaning and spiritual significance. In addition, they can also produce some somatic effects, they can elevate blood pressure and heart rate, produce dilated pupils.

So again this family of drugs includes psilocybin, LSD, mescaline, DMT. In addition to just being used in its pure form, you might also hear about DMT as a component of Ayahuasca which is a plant brew, it's made up of usually two or more different plant substances that can allow someone to take DMT orally. And so as I mentioned, this talk is going to focus primarily on psilocybin assisted therapy as this is the most commonly used classic psychedelic in the modern era that does clinical research with these drugs. And so psilocybin is a naturally occurring tryptamine psychedelic that's found in at least a couple hundred species of fungi. And its hepatically metabolized to its active metabolite, psilocin. And the half-life is just under an hour and usually we see the onset of effects within about 15-60 minutes and once they're there, they last about 4-6 hours before the person is back to or close to baseline again.

And compared to these other substances, one big difference is just their duration of action. So psilocybin is in some ways kind of in this sweet-spot especially when you compare it to LSD which has a duration of action of 10-12 hours, so you can see how this might be a little bit less fussy to use clinically

because it wouldn't require a team of clinicians to be there for 10-12 hours or so. On the other sort of end of the spectrum, DMT when it's used in its pure intravenous or smoked form, the effects last just a few minutes, or about maybe up to about 10 minutes or so, but we know less about the therapeutic efficacy of these shorter-acting psychedelics.

And importantly when we talk about psychedelics, or at least when I'm talking about them today, I'm not referring to other classes of drugs which include MDMA and Ketamine. And you guys might have heard about these; there's a lot of press about them lately, especially MDMA. You might have seen the articles about the recent MAPs Study which showed that MDMA might actually be a very useful drug for PTSD, but again MDMA actually works by a different mechanism—it's a stimulant. And similarly, ketamine is a dissociative anesthetic and so in some cases there are some similarities, especially with MDMA in how the drug is administered and what sort of "container" is used for the psychotherapy, but we won't be talking too much more about MDMA today.

The reason people are excited about psychedelics is in short that the last 20 years in particular have really shown that in the number of smaller studies, that just one or two doses in combination with some supportive psychotherapy can produce really profound and lasting improvements in mood and in some cases addictions. And you might see how that could be quite exciting, right? Because our existing treatments in psychiatry and psychology usually involve long-standing…you know taking medicine every day or having to go to psychotherapy once a week for a long time in order to see some benefit. So they act quickly, they could produce really huge shifts in mood and behavior change, they seem to be pretty safe and they don't require this repeated use down the road.

So the other disclaimer here is that classic psychedelics including psilocybin and LSD are currently schedule-I under the Controlled Substances Act, meaning that right now the government views these substances as having really no clinical benefit and considerable risk of harm with use, and so what's happening now is that we're sort of building this accumulation of evidence to show that there actually might be some significant benefit, but at the time of this recording, they're still Schedule-I.

So in terms of the mechanisms of action, you generally hear about two categories of explanations about how psychedelics work: the biological and then the psychological or subjective sort of effects. And first we'll cover the biological. And it's important to note at the outset that we're still working on understanding what's going on at both levels of explanation and in particular when we talk about the biological mechanisms, we know much more about what's happening during the acute effects of drug action than we do about what's happening in the long-term to help produce or support these long-term behavioral changes that we see.

So again, 5HT2A or serotonin 2A receptor signaling is pretty critical that we know of so far. And we know that if we give somebody like a 5HT2A receptor blocker like a Ketanserin that will block any subjective effects of psychedelics, as far as we can tell. So 5HT2A receptors are expressed in a pretty broad range of cortical and sub-cortical areas of the brain. And we know from animal research that binding at these receptors in layer-5 prandial neurons in the cortex is pretty key to their function. And similarly the claustrum which is the part of the brain that connects the pre-frontal and the sub-cortical areas of the brain is also important to the function of psychedelics, that it has a very high density of serotonin 2A receptors. And so when psilocin or LSD binds to this 2A receptor, it causes wide-spread internalization of that receptor across both inhibitory and excitatory brain cells so it binds and then the receptor just kind of goes into the cell, and a smaller subset of these cells that are activated in this way, that are excitatory

cells, go on to produce a downstream effect that we associate with the typical behavioral effects of psychedelics. Downstream of that 5HT2A effect, we also know that glutamate and glutamatergic signaling is pretty important to the signaling cascade of psychedelics. There have been some rodent studies that show the knock-out mutation for N-glu, R2 or R3 receptor. Those animals seem not to display the typical behavioral things that we see with psychedelic administration. Serotonin and glutamate signaling might be important to some of the anti-depressant effects that we see following psychedelic use. So we know that we use SSRIs for the treatment of depression, which work on the serotonin signaling system and it might be that psychedelics work directly in the signaling system to produce their benefit. And it might also be that downstream glutamate signaling produces some anti-depressant effect in a manner that's similar to ketamine. And it's possible—and we don't know—but one theory is that there might be this synergistic effect that, you know, maybe something that effects both the serotonin and the glutamate system might be more effective than something that just works on just one or the other system alone.

Some other kind of molecular-level things that happen—and most of this is from animal research—there have been a couple of studies that have shown that neuroplasticity might be upregulated in the settings in psychedelic use as indicated by increases in brain-derived neurotropic factor expression. And there's a really interesting slightly newer line of inquiry that's mostly pre-clinical right now that's looking at the anti-inflammatory effects of psychedelics which is opening the door for a whole bunch of new indications, potentially, but again it's mostly pre-clinical, we don't really know what this does in human research, in human clinical trials.

And then the other level of explanation can be thought of sort of on the brain network level. So there is acute destabilization of brain networks. So what that means is functional connectivity, meaning that you know when areas of the brain are firing simultaneously, that suggests that they're probably communicating with one another. At rest there is quite a bit of communication with nearby or topologically sort of proximal areas of the brain, less communication in topologically distinct or distant areas of the brain. And under the influence of psychedelics, at least in the acute phase, there is much more communication between very distant areas of the brain and the connections are much stronger. And importantly, these are acute effects and we're not suggesting that these exact effects would be seen in somebody you know a week or a month after taking psychedelics despite any persisting improvements in mood or other sorts of symptoms. We're still working to understand exactly how these new connections are made, what they are and whether they're actually correlated with long-term improvements, clinically. You might also hear about the default mode network which is a network of areas of the brain that are communicating when a person is just sitting there, daydreaming, going about their business. And the evidence about the default mode network is a little bit more difficult to interpret because a lot of things can cause changes in the default mode network connectivity.

A colleague of mine here at Hopkins has run a pretty interesting study they published last year. He gave 12 individuals who were healthy a dose of psilocybin and he measured them baseline one week after psilocybin and one month after psilocybin—and did find that there actually were some increases in resting-state functional connections across the brain after psilocybin. And he also found, interestingly, that one week after drug-administration when he showed them images of affective stimuli, so faces that are, you know, angry or sad or happy, that there was less amygdala reactivity to those kinds of stimuli. And that goes back to normal about one month after the psilocybin treatment, but you know the elevations in mood still seem to persist at that time.

So a little bit more about just like the psychological types of explanations, so we've talked about the biological stuff and then you know what else, what's sort of happening on a psychological level. And there's a number of different lines of inquiry here that have been sort of looked at in the last couple decades. So we've found that it's possible that the insights that a person comes to during their actual psychedelic experience might be correlated with long-term improvement, so. There was a survey-study that was done and we took a look at what people reported in terms of having come to some sort of insight during their psychedelic experiences being, you know insight about something going on in their life, with relationships…and they found that the more insightful an experience was, the better their mood was following a psychedelic experience. And our group has developed a measure of this that can be used to study this a little bit more down the road.

Another study from our group took a look at changes in personality traits before and after psilocybin, and as you probably know we usually think of personality traits as being fairly stable over the course of a person's life. There have been a few findings that you know something like an intensive meditation practice, or a long-term psycho-therapy or long-term anti-depressant use can produce some changes in personality traits, and we found that in a study of healthy people who took psilocybin, there were higher levels of openness in some participants as long as like a year after the experience. And further, we found that the people who reported a more mystical quality to their experience had greater changes in their level of openness.

And similarly, another study from our group examined the relationship between psychological flexibility and changes in psychological flexibility and how that might relate to changes in depression and anxiety. And one analysis showed that actually changes that people reported in their ability to be psychologically flexible fully explained any relationship between psychological insight or mystical experience and improvements in depression. So it might be actually that it's really just being able to think more flexibly that is correlated with improvements in mood and other symptoms.

Others posit that psychedelics and meditation actually might have overlapping mechanisms and that they can cause similar changes in brain function. There's at least one study that found significant increases in mindfulness after the use of Ayahuasca. Other folks out there are investigating you know whether we can use psychedelics and meditation in a synergistic way to sort of combine the two interventions and make for some kind of supercharged meditation intervention.

And finally here's the "mystical peak" sort of experiences—which is a term that has a knack for making people bristle, especially scientists and clinicians. So it's important to note that when we use the term "mystical" we mean a constellation of empirically measured phenomenological dimensions, basically, and this doesn't imply any sort of supernatural level of explanation, and that these kinds of experiences share qualities with other non-drug-induced peak experiences. In one measure that was developed by our group called the "mystical experience questionnaire" it takes a look at the facets of unity, deeply felt positive mood, transcendence of space and time, ineffability, sense of sacredness or reverence, and we found that it's actually a dose-dependent effect and so with higher doses of psilocybin, people usually describe their experience as having more mystical sorts of qualities. And we also found that the more mystical an experience is the more likely a person is to have longer-term improvements in quality of life and overall mood improvement and things like that. So it's pretty remarkable.

So just a little bit about the history of clinical research with psychedelics and what has happened over the last little over half-century at this point. There was a first wave of research that happened starting

in/around the 1950s and ended in the 1970s. And this got started—you might have heard this story—you know, Albert Hoffman synthesized LSD, it sat on a shelf for a little while, one day he accidentally took it and realized, woah, there's something very unique and interesting about the subjective effects of this drug. The company he was working for eventually thought, well, maybe this can be useful to psychiatrists or other mental health clinicians who are trying to understand the mind and the brain, that maybe this can be a drug that can be used to mimic psychosis, which is kind of what people first thought was going on. And so this company, Sandoz, just shipped vast quantities of LSD all over the world to all sorts of researches who began to work with this drug. And initially you know the drug administration happened in you know maybe like a pretty bare clinical room, there wasn't much preparation about what to expect, people might have been left alone all day. As you can imagine, that did indeed result in people feeling and expressing and showing behaviors that might have mimicked psychosis. But gradually they kind of noticed that yeah, if we pair this with a more psychotherapeutically warm approach, there might actually be some potential for therapeutic efficacy. And there were a ton of studies that were published during this time. Unfortunately many of the studies were weakened by you know poor design. A lot of them were just like a handful of case reports and there wasn't much attention paid to standardizing any sort of protocol or saying exactly how much was used or over what period of time or what sort of therapy happened afterward, and so it was really difficult to draw very many concrete conclusions from that era of research. And around the 60s, research started to die down and eventually went dormant for about three decades due to safety concerns related to non-medical use, you know and folks like Tim Leary really contributed to all this being publicized in quite a negative way. So this went dormant for quite a while. 1999 was when one of the first psychedelic human drug administration studies was published again. That was Rick Strassman's group in New Mexico where he gave individuals intravenous DMT and then shortly thereafter a lot of other centers including our own published other studies with human drug administration with psilocybin in particular. So the first wave used primarily LSD but there also was some psilocybin. The second wave mostly has focused on psilocybin in part due to it being easier to use clinically due to its shorter duration of action, in part just because it has less cultural baggage than LSD. And so this started off in healthy individuals and gradually we've moved into more clinical populations including people with depression and anxiety, secondary to terminal cancer, a variety of substance use disorders, major depressive disorder, OCD and others. And a little bit later we'll talk about just a few of the cursory findings from there.

But before we get into that I thought we might just talk a little bit about just what the general model is for treatment because it's not always clear from reading the headlines and just the news articles about what actually happens during psychedelic treatment. So what happens when you know someone contacts us is interested in participating in a trial, we do a pretty thorough medical and psychological evaluation. This often takes the period of a couple of days to complete. In particular we're looking to make sure that people who have a family history of bipolar or schizophrenia disorder or a personal history of any kind of bipolar or schizophrenia spectrum disorders are excluded because there is a theoretical risk of precipitating mania or psychosis with these drugs. In addition we usually require a person to have, you know if they have hypertension, that their blood pressure be stable because blood pressure and heart rate elevations can happen during the session day. And in addition, in terms of what medications a person can be on, a major contraindication is concurrent use of any kind of serotonergic drug, meaning like any SSRI or most other antidepressants. We're still sort of studying what the exact risks are but in general what's often reported is actually a dampening of the subjective effects of psychedelics when somebody is on something like an SSRI. But theoretically there is a risk of serotonin

syndrome or other more serious complications. And eventually when it's clear that someone looks good to go, they're paired with two facilitators, and so together, this triad—the patient and two facilitators—will spend about 8 hours together. This can be a little more or a little less, depending on the protocol. And during that time they will build rapport, the patient will hopefully feel safe with the two people who will be with him or her during the dosing day. They go over like a life-review, they sort of talk about you know what's brought a person here, what's happened in the course of their life until the present day. There is sometime use of a specific therapeutic modality, and this is more common now that we're moving into more clinical populations, so as an example we might use something like motivational interviewing in a substance- or eating disorder. And they also talk about just what to expect from acute drug effects on the session day. And there's a lot to say here about you know like well who are the facilitators, who should be facilitating this kind of work? And you know we're in a group with a variety of different mental health professionals, and the short answer there is that we're still sort of working this out between the FDA and some of the entities that are doing this research about what is appropriate to have the support for psychedelic sessions, right? Like should there be an MD on call? Does one of the providers need to be an MD? And as you can imagine this is actually responsible for a huge chunk of the actual cost of providing this treatment because to cover clinician time for two people is no small matter. And we don't really know whether two providers is really ideal either. During the pandemic there have been some minor changes to some of our protocols, social distancing. We've played around with the idea of like oh, you know, maybe we just have one person in the room and another person is there monitoring remotely. We don't know exactly, you know, is this really the equivalent in terms of efficacy to a two-provider sort of situation. Part of the reason that there are two providers is in part practical, if someone needs to take a break to use the restroom or grab a bite to eat, we don't want to just leave the person there alone. In some studies they prefer a dyad, meaning one male and one female provider, but that's not the case in every study. So there's a lot we have yet to learn and understand about what is ideal in providing support.

And so what happens on a typical dosing day, the patient will be lying prone most of the day, and they're wearing eye-shades and headphones and encouraged to have an introspective sort of experience. And the facilitators on the session day are there, they're kind of mostly hanging back. They're there for support if somebody is feeling overwhelmed or needs or would benefit from some kind of reassurance or having a hand to hold, but in general we let the person just have the experience that they're having and leave the interpretation and you know exploration of meaning and meaning-making for the days following the drug administration. And that happens during those integration visits, or really they're just follow-up psychotherapy visits. And usually both providers will be there at that time as well. And during this time they're also being monitored you know every 30-60 minutes to make sure their blood pressure and heart-rate doesn't go too high, we have emergency medications there if needed to bring someone's pressure or heart rate down if its getting to a dangerous level; that happens very rarely. We also have emergency benzodiazepine and usually an anti-psychotic on hand just in case, but again it's very very rare that those medications are needed. Most of the time if someone is having a difficult or challenging experience they can be managed with reassurance, and it helps also that we tell them, you know, in the preparation period that this might happen and we provide them with some tools about how to navigate that, and then there just there on the session day to provide in person support if and when that does happen. And it's also notable that having a challenging experience is actually quite common. In some of our healthy earlier studies about a third of people reported a period of significant anxiety or dysphoric mood, but having those kinds of experiences isn't correlated with poor outcomes.

In fact, a lot of the people who did have challenging experiences in this supported kind of framework actually did quite well. The evidence about what happens with challenging experiences in naturalistic use, just out in recreational psychedelic users is a little different. There was a survey study that was done by our group and they took a look at something like 2,000 people who had reported having had a challenging experience just using psychedelics recreationally. And something on the order of 2-3% reported really severe outcomes that led them to seek medical help or in some cases they became violent and obviously being out in the world, maybe in public, would not be an ideal place for that to happen. So this is certainly a safer container.

[Lachelle Smith]

Can you remind us—how do folks getting into this trial? Randomized? Controlled? Placebo? Can we send all of our patients? Talk to us about that.

[Natalie Gukasyan]

Well the placebo control is a whole different story and I'll maybe talk about that a little bit later toward the end, but we're recruiting for a number of different indications. Some of our studies are randomized placebo controlled, some are open label. Folks can check out our ongoing studies and planned studies at hopkinspsychedelic.org. So right now we have a dual diagnosis study for people with co-occurring depression and alcohol use disorder; we have an Alzheimer's study; we have an anorexia nervosa study; there's an ongoing, that multi-site depression study via Usona and there might actually be some sites that are closer to you guys that are not at Hopkins but you can check those out at usonainstitute.org but if you just Google Usona Institute you can find their website and more information about the different sites…but I can talk a little bit more about what the deal is with blinding because you can imagine when a drug has such profound subjective effects it can actually be quite difficult to validly blind that kind of intervention.

So at this point I'll just cover a couple of the studies that have been done for different sorts of indications. So depression, like I mentioned earlier is furthest along as an indication for which psilocybin assisted therapy might be approved. The earlier evidence in the modern or second wave of psychedelic research for any efficacy for mood improvement initially came out of healthy participants. So they found that yeah, like, somebody might have gotten psilocybin and then six months or a year later they're actually reporting, yeah I'm having significantly improved mood and I think it's related to having had psilocybin. And after they saw this they sort of trying this direction out in people who are suffering from terminal cancer who also had anxiety or depression that was associate with that, so sort of like an adjustment disorder kind of picture. And there were three studies that looked at that, and one of them was at our center. And it showed pretty impressive results. And there was actually a recent paper published out of NYU's group looking at what happened in the longer term with people in their study who were still alive. And they found that up to four and a half years out, people were still doing quite well with respect to depression and anxiety symptoms. And eventually the other groups took a look at what happens in major depressive disorder specifically, so it's a little bit of a different population than people who are you know dying and have significant anxiety or depression. One of the first studies was done over in the UK, they did an open-label study of about 12 people who had treatment resistant depression and they found pretty significant improvement in the weeks and months following. And since then there have been kind of more rigorous designed studies and this one was published last year out of our group, we did a waiting-list controlled study of two high-dose psilocybin sessions for major

depressive disorder. So what happened was you know someone would enter the study and they were randomized to either get the psilocybin immediately or to wait 8 weeks and get it after that delay period, and this was to control for any improvement we might just see as a result of being enrolled in a study or just the natural timeline of what happens in depression—you know some people just spontaneously improve. Their Ham-D scores which are rated by blinded clinicians in the delay-treatment group stayed pretty much flat over that 8-week delay period…

[Sam Steffen]

The Ham-D score that Dr. Gukasyan is referring to here is an abbreviation for the Hamilton Rating Score for Depression, sometimes called the Ham-D or the HRSD. It's a multiple item questionnaire used to evaluate the severity of depression symptoms and as a guide to evaluate recovery.

[Natalie Gukasyan]

…while the people who received immediate treatment went down and were significantly different from the delay groups. The people who got treatment immediately were close to on average being in the remitted range, but a total of 71% had clinical response meaning that they improved 50% or better in terms of their Ham-D scores and 58% were in remission one month out. So it's pretty significant, I mean if you know much about effect sizes, effect sizes of two-and-a-half and 2.6 are almost unheard of in this kind of population. It basically means that there's more than two standard deviations of difference between their baseline and their follow-up scores in their Ham-D. So right now we're actually completing the long-term analysis of this, so we followed these people out for a year and we're working on it but I can tell you that it's looking quite favorable that over the course of a year many people continue to do very well, which is incredible given that this is an intervention where people come in, they take a drug, they get a little bit of therapy around it, and then they don't have to take anything on a daily basis after that.

So substance use disorders are another area that has been looked at, and they're ongoing studies. So this was done by Bogenschutz and colleagues over at NYU. They took a group of ten people who had alcohol use disorder, they gave them psilocybin, I think it was either one or two doses—so some people received one dose, some people received two—and they paired this with a motivational interviewing based kind of therapeutic approach. And so as they progressed after their first psilocybin dose, the number of drinking days on average went down, both in their general drinking days and their heavy drinking days, and this also lead to pretty large effect sizes. So right now they're working on a larger study with this group and they're pretty close to being wrapped up with data collection if I'm not mistaken.

And finally, here's another study from our group—this is Matt Johnson and L. Garcia's study where they took smokers and they gave them psilocybin paired with cognitive behavioral therapy and they found that at 6-month follow up, a whopping 80% of them were abstinent. So these are life-long smokers, pretty much, a smoking history of 31 years on average. Longer term follow-up of this group showed I believe it was something on the order of a little over 60% were still abstinent at 12 months. So that's pretty remarkable.

But again, as you'll notice, like, these are pretty small sample sizes—so this is a group of 15. The Bogenschutz alcohol study was a group of 10. Our study that I just featured earlier was a group of 24.

And so really the next step is to demonstrate that this intervention is safe and effective on a much larger scale.

So that's kind of what's going on now. So there are two entities that are currently running these larger phase-II trials comparing psilocybin to placebo for major depressive disorder—that's Usona, who we're working with, Compass, is the other group in this space who's operating right now, and there are earlier phase studies going on for a variety of indications and there's also a sort of interesting new line of potential therapeutic efficacy for inflammatory conditions, which is really exciting. And earlier Lachelle sort of asked or mentioned the idea of blinding, what do we make of that? What do we do? Is that even valid in this kind of intervention when it's very likely that people might become aware of what condition they're in. There have been a lot of conversations I think between the people doing this research and the FDA who will ultimately be responsible for evaluating whether this is all valid and whether they should accept this as evidence that it's better. And I think there are still some concerns about whether something like a pretty straightforward placebo control trial is appropriate for evaluating the efficacy of psilocybin. And there have been a number of different ways that people have tried to control for the problems associated with that, so for example in the Usona study, the placebo condition is actually an active placebo, it's Niacin, which can produce like some physical sensations that might mimic some of the sensations that you might feel with the onset of psychedelics, so it causes like a facial flushing or a tingling. And somebody might mistake that for the onset of a psychedelic experience, especially if they're psychedelic naïve. But there are some concerns, like: is it really even possible to have a placebo-controlled design that's valid, because in many cases it's not just the patients who can tell, it's the study team who thinks that they know. And they've done a couple of studies in which they actually ask, you know the facilitators and the patients, like "Hey, what do you think that you got?" and the majority of times people are able to tell. And you know one thing is that there's—as you might have noticed—there's actually quite a bit of psychotherapy involved and so a lot of the issues that we're bumping into here mimic the problems that have happened in psychotherapy research over the years, is that there's problems of allegiance, you know if a team believes that their approach is better of course they're going to be better at delivering you know whatever specialty psychotherapy that they deliver. So there's a lot of issues, there's a lot of different ways people are trying to get around it. But in any case, you know these smaller studies show there's quite a bit of promise. Whether that's going to bear out in these larger studies has yet to be seen. MDMA which is a related compound but not exactly a classic psychedelic as you might have recently seen on the news has sort of made it forward to the next phase of research, it's going to be moving out to phase III so it's still quite promising and you might have seen there's like a ton of money being dumped into this space, overall, with a lot of private interests sort of trying to get ahead of the curve and sort of get set up for when they believe this will be approved, but we'll wait and see if that actually happens.

Yeah, so key points, just to summarize. Classic psychedelics work primarily, we know the 5HT2A receptor agonism is critical to their function; there's a variety of cell and brain network level changes and we're still trying to understand a lot about the mechanisms behind the longer term effects which are a little bit more mysterious to us. There's a huge psychotherapy component that might drive a lot of the cost associated with this intervention that we're still figuring out exactly you know what constraints are going to be put upon providers when they provide this and we still don't really know the exact optimal setup for delivering this sort of treatment. And finally there are a lot of smaller studies out there that suggest that psilocybin and similar compounds might be efficacious when combined with psychotherapy

for safe and effective treatment of depression and other indications are currently being researched right now with a lot of exciting stuff on the horizon.

[Lachelle Smith]

Dr. Whitaker, I'm wondering if you can help facilitate questions.

[Tara Whitaker]

Yeah, there were two questions:

[Sam Steffen]

Speaking here is Tara Whitaker, family medicine physician at Capital City Family Medicine in Boise. She's also a panelist for ECHO Idaho's Behavioral Health in Primary Care series.

[Tara Whitaker]

…one was around the duration of the treatment session and then just repeating the duration of action of the psilocybin you guys are giving—I know you mentioned that earlier, but also these treatment sessions get—it sounds like they're about maybe up to 8 hours long—but maybe talking about that a little bit more would be helpful.

[Natalie Gukasyan]

Yeah sure, so we usually have people come in around 8 or 9 in the morning, we do our baseline assessments and make sure everything's going to be okay and dose them within an hour, and it's an all day affair. So we're there usually until at least 5 in the evening. We also require participants to have a pick-up person, we never let them go home alone. But it is quite intensive, you know, we're sitting there all day, three people in a room, usually, plus a medical coverage person if one of the providers is not an MD.

[Tara Whitaker]

And what is that like as a clinician, I'm just curious?

[Natalie Gukasyan]

Yeah, it's really interesting. I think it's also—even the stuff outside of the session itself—like the preparation for many of the studies it's like two long sessions, so it's two 4-hour sessions where you're just sitting with the participant, getting their life history and I think it really allows for a much more rapid development of rapport than I'm used to in just you know the 45-minute or hour that I get with patients sometimes. And I do think that's probably underemphasized is really the contribution of how much psychotherapy is really doing some of the lifting here in the therapeutic efficacy. There was another study recently published—this was out of a group in the UK, it was published I think in *The New England Journal*—where they looked at Lexapro versus psilocybin, so they had this double-dummy model where people got either placebo or psilocybin with the usual dosing-day stuff, and then they crossed over the people who got psilocybin got placebo pills every day and the people who got placebo got Lexapro every day and they, both groups actually, had a substantial reduction in their depressive symptoms very soon after the dosing day, so. And I'm assuming that many of them knew, like oh this is probably placebo. The other thing I'll say is that like I'm consistently surprised by what I see in the sessions—you might go in

thinking like I know what this person's going to have, and I'm almost always wrong about what kind of experience they're going to have. So, yeah, we still have a lot to learn about who this kind of intervention's best for and who it can help.

[Tara Whitaker]

Do you have to stop their other psychiatric medications first just for the serotonin concern? What is your approach there?

[Natalie Gukasyan]

Yeah, so they do have to be off of anything like an SSRI and they have to be off for like 4-5 half-lives. And even in some cases you know we suspect that they might do better if they have a longer period of time off. So we're doing a survey study right now just of people who have used psychedelics out in the community about you know, like, "yeah, did you use psychedelics one month… two months… three months after coming off of your SSRI? And what happened?" Because a lot of people say, "I felt nothing," or "I felt much lower effects than I would have expected." So yeah, people have to be off of the serotonergic meds; it's less clear what to do around other psychotropic meds like something like gabapentin or Benadryl or something like that, but it's pretty clear that we need people to be off of the serotonergic meds.

[Tara Whitaker]

And then I guess the other question that came up earlier was around psilocybin and terminal cancer and kind of coping with confronting death and I know that's come up in the lay literature a lot, and obviously that's not what you've been studying, but any more information about whether this would be approved sooner potentially for hospice patients?

[Natalie Gukasyan]

Yeah, I know there's a group out here that's paired with a cancer treatment center that's doing this work there, and I think—you might have heard that like in Canada there was actually approval recently under Compassionate Use License to provide this kind of treatment, so it might be approved for that kind of indication sooner. That's most of what I know. Yeah, it might be a very useful tool for palliative or end-of-life care but we probably still need to know more about it. You know we get quite medically complicated at the end of life, people might be on all sorts of other drugs or be very prone to delirium, and we don't really know if there might be some significant contraindications there in a particular subset of the palliative care population.

[Lachelle Smith]

Nancy, do you want to remind us who and where you are and ask your question?

[Nancy Chaney]

Sure, Nancy Chaney, I'm a nurse in Moscow, Idaho. I'm just wondering with the increased incidence of depression in our society today, people relatively isolated because of the pandemic, you know lots of kind of ongoing stressors in our lives—what do you project will be the illicit use of psilocybin once the success of these studies becomes more widely known, and what does that bode for our advocacy for federal funding and support for ongoing research and advancing this for routine use?

[Natalie Gukasyan]

Yeah, so I think one thing that might happen and is probably already happening is that psychedelics might follow a trajectory that's kind of similar to cannabis, in that there will be patchwork decriminalization or even legalization for therapeutic use of a particular compound. So like in many jurisdictions it's now decriminalized. Oregon recently passed legislation to have psilocybin available for clinical use, which is interesting because like now they have to figure out how to do that. Cause the other thing to say is that like all of our studies, all the studies that we talked about here today, are using synthetic psilocybin, they're not using mushrooms or anything like that. So I suspect there will be much more non-clinical use, it might even be licit, right? Because it will be de-criminalized and legalized, and so we need to probably throw more money into like education and trying to understand more about who is most at risk for negative outcomes and trying to prevent any harm that can come from people who are at the highest risk of using these kinds of substances, so people with you know maybe undiagnosed bipolar disorder or schizophrenia or a family history of those conditions are probably most at risk, and we really, we could do much better in our knowledge about how to help those people. Because that's the other thing is like we don't really know if mania or psychosis that's precipitated by these drugs is different clinically compared to organic mania or psychosis, but this is a very rapidly moving field, so we're going to be seeing movement here one way or another and I would love for there to be more funding to research all the possible risks, cause it's just not there right now.

Music

[Sam Steffen]

That again was Natalie Gukasyan, MD, Psychiatrist and Medical Director at Johns Hopkins University Center for Psychedelic and Consciousness Research in Baltimore, MD presenting "Psychedelic-Assisted Therapy: Overview of Treatment Model and Current Evidence for Efficacy." That lecture was recorded live on June 2, 2021 as a part of ECHO Idaho's Behavioral Health in Primary Care series.

If you'd like to watch the Zoom recording of that presentation, that video is currently available on the ECHO Idaho YouTube channel, which you can access through our website. The Powerpoint slide deck as well as information about how to contact some of the organizations and services mentioned in that talk, are available in our podcast show notes, on our podcast webpage: www.uidaho.edu/echo-podcast

Banjo music

If you're interested in joining our free, live ECHO sessions to receive Continuing Education credit, learn best practices, ask a question or grow your community—please visit our website at www.uidaho.edu/ECHO where you can register to attend, sign-up to receive announcements, donate, and find out more information about our programs.

[Fade out banjo music]

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[cue guitar strum and guitar theme w/ lyrics in background]

We here at ECHO also want to hear your feedback. We welcome your questions, comments and suggestions and invite you to email us at echoidaho@uidaho.edu. And don't forget to subscribe to Something for the Pain using your podcast app. And if you have a moment, write us a review!

[bring up theme song lyrics and chorus until first "echo Idaho", then drop volume and continue playing]

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The contributing voices on today's episode were those of: [Natalie Gukasyan, Lachelle Smith, Tara Whitaker and Nancy Chaney].

We'd also like to thank all of our listeners, without whom none of this would be possible. Without you, we'd just be talking to ourselves.

[Continue to theme chorus, fade]