Are Psychedelics Really Safe No Matter What? Transcript

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Podcast Introduction and Guest Welcome

Every thought you think has a biological effect on your body and mind. Every emotion we have is having physiologic effects in our body. report with the person in front of you.

Are they listening to you or not? There's not a molecular solution to all problems. It can help a little bit. I think that's the real window for psychedelics is they allow that to happen more quickly and more from like sort of exposing what are the underlying things that are happening in your conscious mind or subconscious mind.

Then the faster we can sort get at a way to move forward with it. Welcome to the To Curious MD podcast. I'm Dr. Ali Ahmed. And I am Dr Surya Ravan. With the wisdom from holistic, alternative and these conventional medicines, we are here to challenge the status quo.

We're curious about the connectivity and complexity between diverse fields of knowledge as it relates to consciousness, chronic illness, mental health, resilience and beyond.

learning more about the art and science of healing, or listening to stories of extraordinary healing. You're in the right place. Let's dive in. I'm Dr.

Surya Raman, joined as always by my partner in practice and curiosity, Dr Alia Ahmed. Today we're thrilled to be joined by Dr Kailan Thomas. Kellan is a psychiatric pharmacist who has become one of the most vital voices in the field, helping us bridge the gap between complex psychopharmacology and the evolving landscape of psychedelic medicine.

From demystifying drug-to-drug interactions to navigating the nuances of microdosing and future of clinical safety, Kellin brings a grounded, rigorous, and deeply necessary perspective.

to his work. We just found out as well he is working into impresario mode as we speak and so we are expecting to also have more productions that are in the musical realm and change culture while we're also changing neurobiology.

Welcome, Kaelin. It is such a pleasure to have you with us. Thank you so much for being here. Yeah. And we have so many topics to cover just with that.

I met Kaylin Thomas, he was at UCSF, kind of our cohort, our platform that we had with the Psychedelic Indian Academic Council. He is a PharmD and knows, has an extensive knowledge, I would say, not just about ketamine, but all of the psychedelics treatments.

and he's a professor and teaches at Toro University as well. So excited to have an academic but also somebody who's got this creative arts aswell and brings that perspective into this work.

You are a leading voice in the lens of psychopharmacology. and the research and understanding medication interaction, the role of the pharmacist, which is very vital, especially as we're talking about this course of treatment in psychedelic medicine, often comes up, but often ignored.

The psychedelics renaissance, as now we hope to imagine, is often driven by stories of transformation and healing. As a psychiatric pharmacists, what initially drew you to these compounds?

I would say it started as a precocious teenager reading Alice Huxley and reading lots of essays between Humphrey Osmond and Alice Huxtley. And I didn't think, you know, that could be a career.

So I've just kind of bounced between. I was always interested in psychopharmacology from undergrad level. There were only maybe 20 programs in the country that had any kind of pharmacology undergrad coursework.

So I went to Duke and did chemistry and pharmacologist there and realized that, yeah, this is something I wanted to pursue.

Dr. Thomas's Path into Psychopharmacology

And then I've gone back and forth between like basic science and clinical sciences throughout my career ever since I just learned about Pharmacy, when I was there from someone in my lab, I in Cynthia Kuhn's psychopharmacology lab at Duke, doing research on dopamine differences in neurobiology and just realized that Maybe PhD is not for me, maybe I'd rather do something more clinical degree based.

And ever since, you know, between from Duke to UCSF to Michigan to USC, practicing in Singapore for a year, I've just gone back and forth between basic science and translational science is really always what I wanted to do is to live between those, both of those worlds.

Yeah, I feel like you're the right person to ask this question of because you've kind of seen the broad spectrum. When we talk about psychedelics, when we talked about ketamine, there's this idea of the classic psychedelic and the non-classical or compounds like MDMA and ketamine.

Do you make a distinction between them? Uh, I mean, so yeah, it's a good question. It's whether I'm wearing my sort of pharmacologist hat or my clinician hat.

Um, yeah. There are differences, but fundamentally most of them are eventually getting to the glutamate system. And so it just sort like, how are we having these second messenger systems triggered in what timelines and as gold Dolan.

has taught me there's different sort of windows based on the molecular pharmacology about how they open these windows and critical periods of relearning.

And I think all of that is vital. I really think that we need to constantly think about the therapeutic elements, the psychotherapy with the pharmacologist.

go back to the paradigm of just pharmacology only, it's not going to be that much better. So I think we need to optimize both sides and bring these two ways of treatment together.

And I would say this becomes especially important now as there seems to be an emphasis on research and also the pharmaceutical industry being involved in that realm, taking over kind of the aspect of a drug, of molecule versus the experience and or the and also recognizing that safety and efficacy are just as vital.

So how would that really occur in your mind, or how should it occur when we talk about, you know, psilocybin coming online next year? How should these psychedelic medicines be administered in a safe, supported way without taking away from the natural, nature-based effect and treatment?

Yeah, I think it creates a real opportunity and that's really what my entire career is going to be dedicated to figuring out how do we integrate traditional psychiatric prescribing into this new paradigm of more of an interventional approach with long lasting effects, right?

You know, we've seen from the data at Hopkins, at Imperial College of London that one or two doses, people are still doing quite well, 12 months, 16 months 18 months later.

So that's like my whole, that really all I'm trying to figure out is how to get those to integrate more carefully, cautiously for the optimization of people's wellbeing mentally.

Absolutely. And one of the things like you just mentioned, as we bring those two worlds together, the prescribing and then the psychedelics, and the interaction of them two.

There's lots of different precautions right now about using psilocybin with SSRIs. Deprescribing antidepressants is also kind of on the rise. So how do you see these two streams clashing or interacting?

Yeah, so when I did the CIS 2017 cohort, that was sort of my primary motivation was I heard a lot of people being like, isn't that dangerous? Oh, serotonin syndrome.

I said, well, I've seen for 15 years of prescribing multiple serogenergic agents together. And my mentors at USC and other places had seen zero in their whole career.

So the first thing I wanted to get out there was writing a review paper about the potential risks. And really the risks come when you add monoamine oxidase inhibitors.

My concern is SSRIs and ayahuasca. That's really like one of the only things that concerns me, psilocybin not concerned, MDMA.

Classic vs Non-Classical Psychedelics

We actually have studies and trials that have shown there does not appear to be any risk with those. So it's truly when you stop the metabolism of serotonin and then add serotinergic agents, that's when we get into trouble.

But as you both know, it's pretty rare to see people on MAOIs these days. You know I might've seen one out of a thousand plus people that I've worked with that was taking an MAoI.

But it is something to be concerned about with Ayahuasca because we know they have. monamine oxidase inhibition. And so how do we navigate that piece with ayahuasca is always fascinating to me.

I know there's retreats and centers that have combined the two safely, but they, I think they minimize the SSRI dosages prior to the sessions. and I that's a good way to sort of mitigate harms.

Cause that really for me, from a pharmacologic standpoint, that the biggest interaction I'm worried about. So for our audience then, our audiences are a mixed kind of community of patients, people who are just interested in psychedelic medicine and clinicians and other providers.

Give us an idea of what serotonin syndrome is and what is the harm. And what you seem to be describing is a harm reduction model for treatment. So give us some more information about what that would look like and, what's the safest way to approach this.

Yeah, so the most specific symptom on the Hunter criteria for serotonin toxicity is that in the only case that I've actually seen in my clinical practice at a hospital inpatient psychiatry was seeing like myoclonus at the ankles.

That's a very good indicator of something is awry. You can also see exaggerated deep tendon reflexes. So if you just do the patellar check and you'll see like a plus four on deep tendon reflexes, those will help you distinguish is the serotonin toxicity or not.

And it's pretty rare, but it is something that I'm concerned with because then if get that level of hyperreflexia and myoclonus, you can start to have sort of organ damages, seizures possible.

So those are the things that I would say to look out for from like Hunter criteria of serotonin toxicity. Absolutely. And these are some of the ways in which we're seeing how this relative risk, right?

This risk when certain conditions come together. So knowing that it's ayahuasca versus psilocybin. And then now I want to challenge also on this idea of microdosing.

You know, people are micro dosing psilocybin. And I know you talk about the heart valve and you know how, and I'm really concerned about that as well.

I don't think things that are labeled benign are necessarily always benigned. When we use the word, we kind of minimize, you and say that, oh, it's fine because it is micro-dose.

It's nothing. But I'm really worried about the receptors on the heart valve because, yeah, if you can explain some of that and what your concern is. Yeah, it's funny because I've put this out, I don't know, maybe three years ago or something.

Now I'm seeing it on TikTok and social media of challenging my hypothesis around this. There's been a really excellent paper from colleagues that was just published within the past year that really looks systematically and gives you some nice charts and graphs about different receptor pharmacology, different compounds and what between their binding affinity to the serotonin 2B receptor, which has been implicated in valvular fibroblast proliferation.

So that was really how it came to my concern was, you know, people, if you follow the protocols, like every three days for a month and then take a months off, I think the risk is minimal.

But then I kept hearing more and more people saying, no, microdose every day for year. And I'm like, well, that may not be safe. We don't know. If we don' have any data and no one's looking for it.

That's the other piece that people are like. Well, wouldn't we have seen it? I go, how many people tell their doctors they're microdosing? How many doctors would know to even look for an echo or anything?

So yeah, you feel things like palpitations, shortness of breath. And I've had some people reach out to me since I published those articles and said that they did experience some of those symptoms, but then they stopped and then the echoes weren't high quality.

And so it's very hard. If you're not looking for something, you'll never find it. That's what I learned in science.

Safe Administration and SSRI Interactions

It's sort of a Swiss cheese. You go, well, we haven't seen it, I'm like, is anyone ever had a sudden cardiac death? And who would have looked for that?

No one. They didn't tell their family. They didn't tell their doctors, right? So it's something that I'm concerned and other labs that have better pharmacology credentials than me are also concerned.

And then people look at animal data and they go, oh, we gave it to a mouse for a couple of weeks, so it prints probably fine. I was like, yeah. I used to work in phase one first in human clinical CNS trials and animal data toxicology doesn't always track to human toxicologist.

So those would be my words of caution for as we move forward. Yeah, absolutely. And so we don't have data from 20, 30, 40 years of use constantly. When we do get that cohort, it's too late.

There's this other impact that's to do with ketamine as well. The physiologic long-term impacts of ketamines, do you want to kind of bring that up? Because that is something that we are very aware of, we constantly monitor for and mitigate.

Yeah, one of my colleagues has done pretty good toxicology work around ketamine. And we've seen this in places like London and Hong Kong where it became more of a party drug and people got into ketamin use disorders.

Yeah. It takes probably about a gram a day seems to be the threshold for a long-term like bladder cystitis problem where you're just, you know, people get into really serious problems.

But I think all of the current, especially NIMH protocol or even like one mig per KGIM a few days a week, I don't see that there's any sort of toxicology risk there.

It's really, it really does seem to be a threshold of people trying to intake about a gram a day of ketamine on a daily basis that we start to see more of that.

but that said. You know, everyone's different and maybe some people there's a different risk profile, but I just think most of the paradigms of ketamine-assisted therapy are very safe in terms of regards to bladder.

Yeah. And I wonder about also just to kind of get a little bit more granular on the pharmacology too, because it's more of an acidic drug. It's irritant to the bladder lining, right?

One of practices that's happening when we do administer ketamines is giving that bolus of fluid. And I wonder if that already has some sort of protective element to it, you know?

I would imagine that does help mitigate risk for sure. Yeah, I think. Versus like when we give IM and somebody's maybe, so even thinking about it to that level of administration, but yeah.

No, I think, any type of hydration, if you're not sort of stressed, people aren't, you know, that's been the story with MDMA is that all the stories about, oh, the crash, so I'm like, well, stay up all night, a couple of days, see how you feel.

You're, not going to feel good. So I think hydration being in a calm environment, mitigate so many of the risks of ketamine as a molecule. And it's, again, like, we know so much more about ketamin than we knew about LSD or psilocybin.

It's been, it still is in every hospital in the country every single day for 50 plus years, 60 years 70 years now. So. Well, I often get asked by patients and even other providers about ketamine.

You mentioned abuse, but we also talk about is ketamine a drug of abuse? Is it a physiological, does it lead to physiological and I say physiological or even psychological dependence as a form of treatment?

What are your thoughts there? I think if you keep it in the treatment context, I don't think so. I know, it's low risk compared to many of the daily treatments that we see in psychiatry every day.

When it becomes a risk is if it is like a constant pattern of use, right? If they have access to it daily, then much like almost anything, people can form any type of addictive behavior to literally almost everything, these days.

For me, I don't see it as like higher risk than any other psychiatric medication that we already utilize. It's really just the context and the set and setting in which it's prescribed and utilized.

Well, Matthew Perry comes to mind, you know, his addiction in history and his high use requirement. Was that an addiction of some sort? Yeah. No, I remember seeing that very, uh, followed that story very closely.

And, um, and when I, when read the stories about, oh, are you like, passed out in the hot tub, I was like, he had to be injecting. There's no way you could insufflate enough drug to make you like that.

And then it turns out that's true. His, like a lot of the people named in lawsuit were actually inject him with multiple grams of ketamine all the time.

Serotonin Syndrome and Harm Reduction

I guess the way I think about it is like how many fentanyl deaths per second are there versus ketamine sort of deaths. And it's incredibly rare. Like you really do have to actually inject ketamine to risk any serious toxicity.

It's almost impossible to get it from any other route than direct injections. Yeah. You've got a good liver that works. It's going to keep cranking it and get rid of it for you.

Short acting. Beautiful. All right, Alia, do you have? I do. And I wanted to step back and talk a little bit about what you mentioned earlier about psilocybin, LSD, the classical versus the non-classical psychedelics.

Should they be treated equally or differentially because of the mode of action, being serotonergic, one being non serotinergic? What makes them different and what makes the same?

Yeah, so that's one of the fundamental pharmacology questions that I often think about is because with ketamine, which is an MDA antagonist, they're working on the seam sort of neuron infrastructure in the cortex, medial prefrontal cortex.

And so, there are projections of serotonergic receptors into the glutamate systems. And, so I think a lot of the basic science research that's being done is starting to tease out how those interplay.

So, when we look at sort of like brainstem seratonin neuron projections into cortical layers where we have a lots of 2A density with psilocin, LSD, DMT.

then they project into the cortical layer five pyramidal neurons that have both expressions of NMDA, AMPA receptors that are the glutamate system, but then Cilicin LSD are sort of also integrated into that and production of brain-derived neurotrophic factors.

So I think there's interplay and I, think as we learn about the pharmacology of all these different molecules, there are different timelines, they're different sort of receptor binding, how long they last and project.

And I thing ketamine is sort the most direct that we have right now. But as you look out to Cilicin, LSD, Ibogaine, we might have sort longer and longer ways that these pathways are triggered through second messenger systems.

You just brought so beautifully together that graph from Goldwell's paper and I quote that all the time where you see the lens of action of each molecule and you'll see that critical period opening and just you brought together why that works in that way is depending on how where it's kind of interacting, you can trigger them for longer and longer periods.

And with ketamine, that is a two to three hour, I'd say 45 minute to an hour and a half window, and you've got neuroplasticity for what, 48 to 72 hours.

So this neuro plasticity in that targeted way, in those pathways that you talked about, because they have to do with depression, That's where they're going.

That where that strengthening is happening.

Microdosing Risks and 5-HT2B Concerns

I guess what I want to ask is, did a dearth of that compound there? Is it that we've just kind of found the right key to the lock? Or is it teaching us something about depression and the underlying systems and how we get to that place of depression?

What do you think these molecules are uncovering in that way, if that can be answered? Yeah, I think, like you said, it's interesting if you track the actual duration of the subjective experience of each molecule.

It does seem to track exactly with Gould Dolan, who I consider an absolute genius in our field. Hopefully she gets a Nobel prize at some point. I do think it does track with the subject of experience and then, so then my concern is if We're start to use molecules that aren't having that long subjective experience, like what are we losing there?

Because it seems to very clearly show the longer the molecule can, you know, change sort of default mode network function, loss of ego, insights, whatever the case may be for it.

I think if we just look too closely at the molecular pharmacology, we're missing something about meaning making and how long people need to experience and sit with discomfort or whatever's coming up for them.

And then how do we integrate that back into their sort of daily life practices and actually start to modify the behaviors that got people into a state of mental health crisis that they're in.

So I think it is very important to notice that the timelines for how long the symptoms improve seem to be very directly related to the duration of the subjective experience for psychedelics, whether that's ketamine to Ibogaine.

Yeah, which so goes against like the microdosing protocols, right? It's two separate ideas. It works in a small dose too, and it works through a subjective experience, so it's so confusing.

And Ibogaine, I know people are micro-dossing for various reasons. I think I want to bring it together a little bit too because Ibobaine is the most powerful one.

And we haven't yet, and I think this is fair to say, we have yet uncapped or totally revealed all the different use cases for these medicines. We're not even close.

You know, it's kind of like the GLP ones. They got them, then they started figuring out all these other use-cases. And I wonder if we're going to see that with like traumatic brain injuries and spinal cord injuries.

I mean, what do you see or what's the signal in the research maybe? Yeah, Ibogaine to me from a pharmacologic standpoint is one of the most complicated molecules that anyone like Hamilton Morris talks about this a lot.

It's just such a unique sort of chemical structure and the pharmacology of it. And we're just barely starting to understand it at this point. Um, but then yeah, the whole microdosing phenomenon, it's just seems like cognitive dissonance to me when people are like, I have somehow hacked the system.

And I'm like you're using a Sandoz molecule from the forties that no one really actually studied. So you using the big pharma molecule, taking it every day with no data at all.

So the LSD microdosing, I just don't understand what people are thinking and why. And most of the data has shown that in any of trials thus far, there is no benefit, really.

There's no efficacy. You know, from a harm reductionist approach, I just want people to be aware there could be risks with it that are very real. So I focus on that, but yeah, there has been indigenous use of peyote, for example, on a microdosing basis.

Like there are people that have used that in that way. And interestingly, mescaline does not have. the serotonin 2B receptor affinity. So yeah, like Ibogaine, we don't know.

Again, I think we need to also think and learn more about indigenous traditional use and sort of integrate that into research protocols because turns out people figured out a lot of stuff thousands of years ago that we didn't recognize.

Oh my gosh, you just mentioned something because that's a vision, right? That's the something to put our visioning to. So knowing what you know, and we've both been in, lots of research studies and clinical experiences and things like that and recruited people for clinical trials, there's certain way we do things.

It's like, oh, you want a clean data set. You want the data to be as homogenous as possible. There's a real reason to keep it clean and demographically, so you can draw population level outcomes and insights.

Ketamine Safety, Toxicity, and Dependence

Here, we're talking about kind of on a personal level. And let me add to that. It has to randomized. All of that, right? Don't blind it, yeah. And how do you even conceive of that with molecules which literally alter the consciousness of the subject taking them?

You cannot blind it. Yeah, it's a big challenge. I mean, my colleague and friend Bilal Zighedi has written a lot of papers about this concept of, you know, functional unblinding and how could you control for that.

But yeah, It's very difficult. The funny thing is like, we don't question it around SSRIs, even though there's clear psychotropic effects that people can detect from taking an SSRi.

But now it's become this big deal for the FDA that they have to grapple with. This changes the way that we think about randomization, unblinding. But to me, it really just, does it work or not?

Like, what are the outcomes? Is it doing what we hoped it did? And is it causing any harms? If not, just let it go. Yeah. Dr. Aiman and I were talking today just about this.

Do you want to bring that up, Aya? We were just talking about. Well, we were talking, I think we're talking the placebo and the nocebo effect. And I this is kind of what we are alluding to when we talk about giving a substance and we do this with SSRIs.

Hey, you're going to take this medicine and it may help you with this. We're already kind-of biasing that patient's experience. In addition to, that the placebo effect is also an effect.

It also has a spiritual, emotional effect, and why aren't we looking at that as a source of understanding what actually does happen at the cellular level that involves this unknown placebo affect?

And to the opposite end, the nascebo effect was what we're seeing with SSRIs. We are seeing a placebo effect, a negative effect. We're seeing all the side effects of chronic use or overuse or incorrect use.

Tell us a little bit more about what your thoughts are on placebo and nocebo effect in psychedelic medicine. Yeah, as I used to tell my clients in inpatient psychiatry settings, when I was, you know, give like medication education groups, I would say every thought you think has a biological effect on your body and mind.

And so like nocebo, right? Everything, every though, t every emotion we have is having physiologic effects in our body. Right? And, so I think that. Yeah, the intention and there's also been data showing the rapport with your prescribing clinician is more predictive of outcomes than whatever medication you took.

So I think there is room for all of it, but that's sort of how I. Think about that as like every thought I, think every action I take has a physiologic response in my body.

And so, yeah, it makes sense to me that there's no SIBO effects. There's rapport with the person in front of you. Are they listening to you or not? Like, there is not a molecular solution to all problems.

It can help a little bit, you know, just like if you… The other thing a lot of my colleagues would talk about SSRI is like, if he broke your ankle and you can't walk, like you have to just stabilize it, right?

That's the way I think about antipsychotics, antidepressants. If you're in crisis in a hospital, you are not able to take in information. You're not really processing things.

And so you need something to sort of hold that cast in place. And with SSRIs, does that mean you need it forever? I don't know. I know each individual could be different, but certainly if you're in the hospital, you may need for some timeframe until all the other things, exercise, diet, nutrition, behavior can shift.

And I think that's the real window for psychedelics is they allow that to happen more quickly and more from like sort of exposing what are the underlying things that are happening in your conscious mind or subconscious mind, then the faster we can sort of get at a way to move forward with it.

So that's the way I, you know, people always think as a pharmacologist that I just believe all medication is the only way. It's furthest thing. The more I've learned, the less I believe in that.

That's amazing. That brings us to our earlier conversation, Aliyah, where we were looking at how do you represent what we're seeing in our patients as data?

We have the typical way of doing these trials and they're running, but what you just described, how we measure that? How do we measure the aspect of what was it to, for that first intake to be a really thorough, therapeutic intake where that's part of the model is that you get to.

I mean, you know, I can talk about your healing center, Alia, is like a patient gets to in a container over the course of 12 to 18 months.

Psychedelic Experience, Meaning, and Neuroplasticity

which none of these trials are running that long, you know, of being able to see the similar therapist, do different kinds of work, move from phase to phase, kind of see that up and down kind happening because the object is to get the patient to where their outcome, what their particular outcome is.

And that's not something that we can put into a clinical trial. So where do you see these models kind maybe blending into each other a little bit or starting to kind to talk to each Yeah, people are starting to use more mixed methods models where they look at qualitative outcomes more than quantitative.

Cause yeah, to quantify everything, maybe that's not important. Do you need some level of quantitative data? But when you start to, you know, I think qualitative measurements have gone a long way in psychedelic trials because it's the first time you have to think about, well, what's this person saying?

What do they actually believe? what is their meaning to them? And so, yeah, a lot of my colleagues are working on more advanced qualitative methods, and you can.

You can look at the language they use, you look that, score it all, or you could quantitate it in various ways. But I think those methods are still sort of emerging to get the best practices of what's accurate, what actually predicts mental wellness.

So yeah, those are definitely important elements that people have been working on. You know, what are we tracking qualitatively instead of just, you know what's the score on the Madras or the PHQ9?

Right. Because those were the surface elements, right? And psychedelics and this work we're doing get to the deeper elements of who am I? What's my purpose and meaning?

We haven't figured that out. Other than the experience questionnaire, which I love, thank goodness thank you Roland Griffiths. Because that gives us some grounding.

Let me just pause here because we actually did a clinical study at our center on five women around the same age in that perimenopausal kind of premenopause state coming in with comorbidities, which we could outline multiple GI, endocrine, cardiac, and all of the systems in the patients we had.

So they were kind complex. They had treatment resistant depression. and they completed a group ketamine experience over six sessions. And we had, you know, their pre-assessments for their clinical scale.

We tracked those scales over the course of their treatment, and we were able to capture that data. What we also

did—and this is where the skills of narrative medicine, I believe, come in, in what you described—is we were able to, you know, document their language of their experience through the course of those six sessions.

And what they said and how they felt and what their experiences, what the experience, how the describe their expenses and they're able bring kind of the meaning making of that and documented their words, their languages.

And using qualitative assessment techniques or, you know, able to code for the language and what we were able observe in comparing that to the mystical experience questionnaire was that most of the patients had the either identity or, you know, reprocessing, re-experiencing kind of in a holistic way their trauma.

So their story, there's a theme for each person's experience based on what they described. And also, by looking at the mystical experience questionnaire, we were able to say, well, Keringin seems to have this signature effect.

It tends to, because it's an inward experience, they tend to disconnect from that sense of reality, right? They feel connected to something else besides their, you know, their not really, the have that dissociative effect, so they can disconnect and they are able connect to there is this idea of them losing a sense of time, right?

Because there's that dissociation. And so it had this signature effect of all of the patients. They all categorically described this out of five questions of The Mystical Experience Questionnaire, which I said, oh, that seems interesting.

It seems to be a ketamine thing. How would you describe the type of experiences that patients have, say with psilocybin or LSD or Ibogaine and ketamine in that type experience with the mystical experience in mind.

Yeah, I think they can all get to the same place. A lot of it is just dose dependent, right? Like the 0.5 mg per kg. Most people are not going to have any type psychedelic experience from that.

But if you get to one or 1.25 or one point five make per keg of ketamine, then you will. And as I remember in my CS program hearing Stan Grof say, he's like, yeah, when I took a lot of Ketamine I was just like a boot on a person's foot.

You don't often have that with classical psychedelics. Yeah. So it's very transpersonal, you know, John Lilly got into thinking that he could talk to dolphins with DARPA funding and all this.

So I think they all get to the fundamental same place. It's just slightly different. It's like the way they activate receptors is a little bit different and timelines and everything.

But I think even just as someone, when you live in your normal state, quote unquote, of consciousness, anytime you can be like, whoa, there's something else?

How's that possible? I think that in and of itself really gives people a lot of freedom. They feel like their consciousness is more autonomous than they thought.

But if you've never experienced that, it's hard to imagine or conceive that that's possible.

Research Methods, Placebo, and Qualitative Outcomes

That's beautifully put. It almost gets to the idea, the spiritual idea that Alan Watts brought up, which was, you know, when you get the message, hang up.

And you just got to a message which is the realization that something is beyond our frames. And that we can get out there and back in a safe manner and that all these molecules take us there in different ways.

And the experience has something to offer us, whether it's growth, perspective, change, a break from a stuck mind, ruminative mind of a depression or a trauma.

That's just kind of recurring over and over again. And that's that break to freedom that comes. Let me like kind maybe telescope out one more time. I'm going to ask you, now we're in 26, as we start to kind land on this really beautiful, intricate and very deep conversation.

Where are we in this quote unquote psychedelic Renaissance? I think Alia and I are definitely more newbies to this Renaissance, I would say, because we're coming at it from the medical field.

We're getting into it kind of in the last maybe five to seven years. I don't know about specifically about you, Alio, but and also kind seeing like there's kind like an ebb and flow.

There's one step forward, two steps back. we've experienced that a couple of times. You know, just like the stigma of this, the big cultural change that needs to come for these to even become part of the conversation that a regular psychiatrist may have with you in the office, although if you live in California, they're already having it.

So it's like a different, we live a little bubble here. But where do you see the kind of field going? I know you're deeply entrenched in the research, but I'm sure you have an understanding of the greater field itself that might inform our listeners.

Yeah. So Taryn's, we can as counterpoint to the Watts quote was, I just keep getting too many messages. So I'm probably more in the McKenna camp and McKinna also said, it's just going to keep getting weirder and weierder until you have to talk about how weird this is.

The whole human experience and as people start to interface with computers and it, that's Our brains are not built for the level of technology that's coming at us, like our hardware is not caught up to the wetware or the software and it's going to be a very challenging next few years.

But I think, and I visited your clinic, it is beautiful and we just need to ground people in physical reality and give them space to really connect with people in a one-to-one thing.

I don't think, as you were saying with narrative medicine, I think homo sapiens would have survived without storytelling. read a lot and think a little about my sort of Druidic lineage where they didn't even write things down.

Like you had to be one-to-one, spoken or sung or played music. And that's why the Romans slaughtered the Druids so quickly was because they could just erase and rewrite an entire thing.

We're seeing this play out, like we've never, we're still in the Roman Empire, unfortunately in America. And so I think that these are the things that we need to connect with people locally in your community as much as you can and be present and show up.

That's how it took a couple hundred humans to survive anywhere on this globe for as many millennia as we've been alive. Well stated. Sometimes I feel that in the broom when we're doing all this transformational work, number one, that it's even possible.

It's like an everyday miracle to get to do this work. What? The human mind can survive even this? We see some of the most treatment-resistant cases, the ones that have lived for years and years having zero hope and they're coming to this, and we see them change, you know?

And you're seeing it in the trials. So it's just like, when I first entered this field, I was like why is everybody else not talking about this and as excited about it as I am?

Because I'm like if you have this why would you not run with it? You know, like for me, it makes no sense that ketamine is in every single emergency room.

Every single OR and the indication for suicidal ideation is not included. That's just malpractice at this level. So we've had this data for a while. Anyway, to see how systems might change.

Any thoughts on that, Kellen Thomas? I mean, the colleagues that I have will go to ketamine quite quickly when they're like, we're not sure what's going on, but let's just start there and see if it calms people down.

Because like you said, yeah, whether it's suicidality or substance use, whatever. It may be, just give that window, that's a window to start, and then you figure out what's going on from there.

So yeah, I think it should be much more widely prescribed, you know, compared to haloperidol, Ativan and diphenhydramine, maybe ketamine. I've had ER docs anecdotally be like, yeah they were combative, they had hit multiple nurses, gave just a regular dose.

They laid down for an hour and they're like oh wow, my bad. Like, you know, so it's like, we're just not- Versus restraining. Yeah, restraints. Calling the, security.

Exactly. And just trying to, I mean, that's the trauma is really that. The system itself isn't traumatizing. I hear these stories every single day. Me too.

You know, one of my questions is, well, if psychedelics are in nature as they are, should we be doing treatment psychedelic medicine facilitated or is recreational okay too?

And, you know there's some cultures that would microdose on this as a medicine, as something to help as we caffeine, chocolate, whatever. You can think of all of those things that are practice.

What would be the benefit of just saying you know, recreational use versus qualified facilitated use and using psychedelics. Yeah, I mean, you can see a lot of cases of recreational where there's no change, right?

Or it maybe even enhances bad behaviors.

Mystical Experience and Clinical Signatures

And I think it's really just all about the intention and the container set and setting of all this that can create and change the dynamics of benefit versus risk.

I don't, again, All like everything needs to be clinical medicine. No one should ever be allowed to use it. I gave the testimony at Oakland city council that it should be decriminalized because what right do I have as a medical practitioner to control other people's consciousness?

Like that's something that I'm very averse to. Just want to provide resources or education so people understand what they might be getting into. Um, and then, you know, Being in a hospital room versus out in nature, like you said, if these medicines were utilized in the natural context, I hope that we get there where retreat centers will, yeah, sure, we have qualified people to reduce harm, but then we're in, you know, the hills of Oregon, for example, or seeing trees in Oregon.

And that there's that sort of back and forth and we need, we definitely need more connection to the land. I mean, I live on unceded Ohlone territory here in Oakland.

And I've read a lot of books about tending the wild and this concept of. You know, whatever we think we have here was because our ancestors were very carefully looking at land use, taking every plant, every animal, everything in the environment and symbiotically integrating with it.

And that's a lot of what we've lost. in our current sort of war state, constant state of wars. It's not a healthy way to live, it's unsustainable, It'll never work.

There's never an end. So the more we can get back in touch with nature and, you know, in Oakland, like Lake Merritt, You can still find the spores from the dead era, the Grateful Dead era playing in the Oakland Coliseum.

It's still there, people still tend that. People know a lot of species around the lake. And so the more we constantly look to natural settings, I think the in tune we can become with systems and be more symbiotic.

You even brought up this really beautiful way of thinking about medicine that comes from the land, is tended to with the Land, it's a different perspective and an energy to the medicine.

And we always talk about this because every medicine kind of has, seems to have a signature. You know, ketamine has its dissociation signature, you know.

LSD brings with it its own signature of the 60s and cults, and things like that, Um, and then you just brought this beautifully where decriminalization coming back to the land is regenerative, not just for the line, but for people and that the medicine that is then born there is of a different kind.

Do you see that like you've got your pharmacist pharmacologist mind that looks at the molecule and says, well, the molecules the same, there's an objectively the say molecule coming out of all these different strains of.

psilocybin, but then there's people who say, well, when you have a different strain of psillocyben, that's called a difference thing and it does a differently, you know, there is shakthi and there are tidal wave and all these different types and people are now kind of even looking at the, would you call it the spirit of the medicine?

Even the land, right? And that is how the indigenous look at this medicine, So can you speak a little bit to that? How, as a Western-minded material mind, can we kind of bring in those ideas as well?

Yeah. It's a very different epistemology of if you're, you are sort of stuck in this scientific reductionism that it's just this, it is just that, we have to taxonomy, classify, and then you later, they figure out, oh, that's all wrong.

Actually, That's not the same strain of cannabis or it was not, the strain, same of this. Yeah, exactly. It's, this is constant. There's sort of a colonial instinct of classifying taxonomy that we always learn later is wrong.

Right? Like that's actually the history of science and from the Western lens. And so I think we need to, yeah, start listening to other perspectives of there's animism, there is a spirit to everything, you know, even what were fungi, were rocks in the past, then became fungi.

So it's like, we don't know. We're the youngest species compared to the rest is the natural world. And the Natural World doesn't need us. They'll figure it out.

Like they don' need as humans. Where we're late to game and we need to be better stewards of the land, really, ultimately. I noticed that ketamine, and I say this to patients, ketamin is just a molecule.

And you're going to get a medicine, you are going dose it this way. But this medicine as ketamine has a unique effect on you when it's even given on that dose.

The Psychedelic Renaissance and Cultural Context

And that goes so you could get the same dose on another day, and it would do something completely different. And it's strange saying this as a physician, because we're trained the opposite way.

We're told, hey, you're supposed to take this medicine. It'll reduce your depression. You know, most patients, 80% of patients reduction in symptoms, first course of treatment.

And it doesn't. And then you're like, huh? So was it the messen or was the person? You know, but it's the interaction of that molecule in that system and the source of it and how it is making its contact with your thought, with you emotion, which we don't have the answer for.

We don' know. That to me is still like hard to explain to people. Like I could give you the same dose and you're

going to have a different experience.

Sometimes people ask me, did you give me more or less? And part of what I'm noticing is where their nervous system is based, you know, when we start. Maybe there's an aspect of that.

And even as you go through the second and the third and fourth session, there is a softening. They're becoming more used to it and maybe they're allowing it more.

But what is that concept of allowing the medicine and fighting the. Can you explain that a little bit just from your perspective and what you've learned?

Yeah, I mean, seeing, you know, people in various altered states, whether that's through psychosis in an inpatient setting or psychedelically induced, or I think our consciousness can shift all the time, based on so many factors in our environment.

And it is a challenge because even the, well, there's challenges. I wrote a paper, the California legislation was trying to set legal limits for every medicine.

And I'm like, you can't, like this is complete nonsense. Like they'd be like you're going to have 10 of this or a hundred doses of that, or this many grams of psilocybin.

That grams psillocybing could be tenfold higher than you think or ten fold lower than. And so to me, yeah, that's a really big challenge for informed consent for people in trials and things is we don't know like, well, this is going to affect you.

And like you said, it could be different next week than it was the same dose the previous week. It's definitely, we have actually quantified the exact milligrams, but it's something that is just changing the way that your entire consciousness operates.

in a way that's always somewhat unpredictable. And it's very difficult to tell day by day how it works. But again, it is the range of human experience, right?

The big fallacy for me as someone that has practiced in psychiatry for this long is that there's some sort of quote unquote normal consciousness. I'm like, you have no idea.

how the person next to you is processing this world and you don't have the same range of experiences or every sensory input, how you make sense of it.

It's highly variable, more variable than we give it credit. And so then when you add molecules, it gets complicated. That's beautiful. So MDMA didn't get to pass-based.

FDA has guidelines, phase one, two, three. Are we ever going to be able to get anything approved with FDA? Yeah, we will. Yeah. I think, again, I want some of the challenges of having a sort of nonprofit entity enter this space as someone that's worked with phase one, CNS, global clinical trials.

It is very serious business when you deal with regulatory. I don't think the FDA has a resistance overall. At any given time, the people on review committee have different perspectives.

And so I think it will get there. They looked at the data and they said, there are some things that we expect, you know, I don't love it, but corporate entities have been in this game for 50, 60, 70 years.

And they keep everything to perfection. Like I've been behind the scenes of phase one trials. The amount of data, the amount people involved is staggering.

So for me, it's not that surprising that just letting therapists collect data at their sites did not quite meet the level of

approval. But now they've got the people that, you know, solve the S-ketamine approval process involved.

It's going to happen. So let's branch to this. Spravato and IV ketamine. What's the difference? What are the similarities? Does it work? And why, you know, and it's provato.

It's pharmaceutical. I say it is a pharmaceutical product. You know all of that. And we have this ketamine, which is… Receive it. Ketamine. Receiving ketamines.

One works different or the same. What is their efficacy comparatively? Yeah, so it's interesting because in Europe, they've had esketamine approved for quite some time and a lot of the groups that were giving oral es ketamine and things, that's where we have a of our pharmacokinetics data.

So there's differences in potency, whether you're measuring analgesia or subjective effects. So, dialing that in is going to be a challenge, but I was just actually at a psychiatric conference virtually today where there is a group that's starting to investigate esketamine versus ketamine intranasal.

And I asking, well, what's the dose equivalence? How would you do that? And to me, es ketamin is pretty variable. When you even look at their own FDA labeling, like intrapatient variability, Anytime you introduce insufflation or oral, there's variability in terms of absorption.

So IV is going to be the most reliable, right?

Recreational Use, Decriminalization, and Nature

I can tell you the pharmacokinetics, it's going be same every time. Whereas with insuflation, you can even look at the esketamine-sparado datasets. You'll see this variability, in term of the percent absorptions.

So it's just a challenge of dosing. And that's why, you know, I know you have my materials of trying to quantify and use bioequivalence data to show like, what's the estimation of this route versus this router versus route.

But it is all an estimation. Individually, there's still variability. And one of the other questions I have is like neuroplasticity, right? If our goal outcome is neuro plasticity and a change in the way these networks are going and firing, there could be a slow boat and then could we have a slightly speedier boat.

You're gonna get there, right? It's just right now when we're trying to serve more people and make sure that we create these pipelines, thinking about where somebody fits and how quickly to get them through.

We're talking about now, even reducing the timelines for trauma treatment from like three years down to like 18 months or something like that. And so, yeah, esketamine is a…

is a very interesting kind of, because when it first started out, I was like, oh my gosh, they did this because they can't redo the trials on racemic ketamine.

Yeah, it was a cash grab. It was generic. I gave that testimony in Oakland City Council because they're like, the biggest pushback is we get is, we have approved medical ways to go.

It's $830 a dose when the molecule costs a dollar to produce. So to me, like I've always seen at studying at Duke, UCSF, there's a lot of games that are just hyper-capitalism that have nothing to do with anything evidence-based or health outcome.

Yeah, and taking out that L enantiomer, what does that do? If we just talk about S-ketamine having one enantomer versus IV ketamine, having both the L and the S mirror enatomers.

Taking that out, how does it affect the difference between the two? Yeah, I mean, it does seem that S like from subjective and analgesia data is slightly more potent, but who cares?

Like why, you know, anything can be dosed properly if you just know what you're working with. And then you insufflate it, so then it's all crazy. It never had anything to do with anything except for capitalist instincts.

There was no reason, there's no medical or pharmacology benefit I could ever conceive of to isolate. Does the l-enantiomer have an effect as well or the metabolites as such?

Yeah, so they did. They've done some studies on R Academy and they were like, oh, maybe this is better. We don't know. No. They're so similar that it's really just about the dose, the intention, and the setting.

All of those things to me are more important than any molecular, especially when you're talking about enantiomers. They are so close, they're binding to the receptors.

You could run these visual models of the exact protein residues, that are all binding in the pocket. So it's like basically putting a lot of attention on something which is kind of a qualitatively very minute difference.

I think so. Expanding it and finding a market in it. Exactly. That's what happened with Spravato, yes. We recently started using Spavato because it is FDA approved for treatment resistant depression.

You have insurance. And access is the key. And a lot of people can access it only through that. Access is key, and I have been surprised by the, like Simi said, how fast you want to get there.

How effectively do you wanna get that? Are you kidding me? We know, we have data. We've done thousands of sessions today. Spravato possibly could get there.

It takes a little longer. You know, maybe it's variable in, you know how you take it in and it is all up to you anyways, right? And I'm surprised to see yes, we're actually having positive results.

However, it set and setting always. If the set and setting, if you're giving Spervato in a chair in the clinical setting and you are giving it in therapeutic supportive way with guidelines with, you know, a soft touch around their treatment, your result is going to be different, 100%. Absolutely.

Yeah. Right? Yeah, from a pharmacologic perspective, the maximum dosage of Sberato approval is under dosing people. Yes. Statistically, I would say. Cause, because especially given absorption possibilities of like percent, like 10%, 20%, 30% lower than you think that will get into plasma concentration.

I think it, it's unfortunate that was the way that it was approached to me because I. Think you're, we're sort of not even necessarily always hitting the 0.5 mcg per kg IV that the NIMH established the basis for its approval on.

So that's sort of my critiques around it. But again, like you said, we live in the systems we love in and people need access. They need coverage. Medicine has become, you know, one of the biggest drains on the US economy.

And it's not because it has to be. 33 other countries in the world figured it out, but it's just the system that we live in. So I think every access point for every client you see needs to be available and considered.

And I appreciate how much you've done in your clinic to allow every possibility for Every client because everyone's different. It's not a clinic. Yeah, it is a healing center.

I agree with that. So we're going to do something fun now. We're gonna do rapid fire. So I have some questions here. And then we'll close with a question.

Molecule, Set, Setting, and Individual Response

As we, and so while you're thinking about these questions, I'm going ask you, want you to think of a questions subconsciously about what makes you curious about this work.

Or you can ask us a curious question, most misunderstood psychedelic. Most overrated psychedelics. LSD. Most underappreciated psychedelic. Pilosibin, I think.

Biggest psychedelics myth. That they're safe no matter what. One indication where the hype exceeds the evidence. I mean, LST for ADHD, and I knew that would fail right off the bat and it did.

It failed spectacularly. Why did you think it was going to fail? Microdosing for ADHD. Yeah, why did think I was gonna fail. Uh, because I think it's people who have a certain range of consciousness in the tech world and Silicon Valley that I live in, that anything out of just like hyper-focus felt somehow productive, but that's a very small percentage of the US population.

So I was like, LSD for ADHD does not, microdosing is not going to work for that. Know your population, makes sense. Absolutely. So now questions around your pharmacology expertise.

Most misunderstood receptor in psychopharmacology. Serotonin 1A is still unknown about how these psychedelics are intercepting with that serotonine 1a receptor.

The most common misconception among physicians about psychedelic? That any serotinergic drug will have a risk of seratonin syndrome. Oh, boy. And then do we need more efficacy data or more safety data?

Definitely more safe data. And one technology that you think will transform psychiatry? People studying humanities more than science. What's your favorite science book?

My favorite Science book probably is, I mean, APA textbook of psychopharmacology has been very helpful for me. Cool. Love that it's a textbook. your most influential mentor?

Probably, I would say, was Cathy Giacchimini at UCSF when I thought about the idea of tracing pharmacogenetics from each lab was just looking at one receptor.

And then she asked me to look at some of the Kaiser psychiatry data sets and I go, you know molecules go through enzymes, transporters, receptors, and she's like, yeah, come to my lab and do that.

So that was very influential. For her to trust me to that, now she's the Dean of UCSF. So she is my most influential mentor. And love that she a woman.

Coffee, tea or neither? Coffee. Well, those are my questions. Now for your turn, as you were thinking consciously, what did your subconscious mind come up with?

I mean, yeah, it made me, a lot of these questions, It's all these moments, right, throughout your training or education that can be such a light switch.

So I had those moments with Duke, with Cynthia Kuhn, asked questions there, Kathy Giacchimini, Vicki Ellingrod. Now they, I was the first in their labs from my pharmacy school and now they're both deans at Michigan and UCSF respectively.

But just being curious and listening to people around, you have the same instinct with my own students, so I'm like, If you have a question or you an idea, let's talk about it.

Let's figure out what you want to do. But what I'm concerned of is I see fewer and fewer people with questions. People think they have the answers or they're just like, just aren't curious anymore.

I don't know. So I've had so few students that want approach and ask curious questions, but that's the way I got to. Do my job was having those questions with mentorship and people around me that were And again, maybe it was rare then too, I don't know, but it just seems like the way that we've commodified education, it's become like people think they can just buy the education.

And it says, you know learning is about engagement and direct interaction with material and people. Oh my gosh. Then the question that comes, well, what is it about not asking questions that's changed in our society?

Why aren't we asking those questions? Well, so I read, you know, both Orwell and Huxley growing up.

Spravato, IV Ketamine, and Access to Care

Right. Bring it back to the circle. Unfortunately, we have the worst of both their predictions, which is we a top-down sort of surveillance mechanism, but we also have information overload to where people just like can't get through the amount of information coming at them per second.

And yeah, I didn't predict that. I thought it would be more Huxleyan, but unfortunately the world continues to get more Orwellian minute by minute. Yeah.

Very cool. And this is why you need the humanities people to understand. Some other books, not just science books. To inform the science, we need the humanities to understand because that is such a beautiful kind of synopsis of, yeah, to be able to step out of your frames of reference to think audaciously.

You need permission, mentors to give you that permission but also to have enough curiosity and have familiarity with different knowledge systems to like, wait a second, there's a little gap here.

Or has somebody put these things together? And looking around going, no, nobody did, and there you go. Those were those breadcrumbs along the way. And that's how we get to these impossible solutions, or that how you get these intersections where we have such a beautiful conversation.

I just have to say, today's conversation really brought in so much into it. Thank you. The childish wonder that the child is, the four or five-year-old, you know, who's a childish wanderer, he's asking questions.

They're asking. Questions galore. That's the question is why does that change? How does it change in a culture? Put you on train tracks and then you go, wait, all you need is food and shelter actually.

Like everything else is made up. Someone else made it up And you can, you may or may not accept it. It's actually up to you. Your consciousness is your own.

So the conscious sovereignty over your consciousness to learning and curiosity and just such a wonderful example of also how we can get to the really interesting synthesis area, the place of synthesis of different knowledge systems and really arrive at new pathways ahead.

Reading it all together today. In our next episode, Kailin, we're going to talk about music. Oh, great. And pharmacology. Music as pharmacologist. I get jobs and paid from my science, pharmacological, medical knowledge base, but I know more about Music and art and literature.

than I know, but no one pays me for that. Let's get you one for the episode. Nobody pays you for it. That's the second episode! Yep, sounds good. I love that, thank you so much.

So keep it out in your email, we'll be contacting you. Sounds good, and thank for this conversation. Thank you, appreciate so, much keep up all the great work you do.

Thanks for joining us on the Two Curious Andy podcast. We hope today's episode inspired you to ask new questions and explore fresh perspectives. We challenge you to ask us those unasked questions that you're curious about in your medical practice, condition, health and wellness.

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