Dr. Manish Agrawal Delivers Grand Rounds at MedStar Georgetown University Hospital

Psychedelic Medicine–History and Clinical Research

January 30, 2025

Full Transcript

Manish Agrawal:

An opinion piece from the *New York Times*, *'Is Everyone High?'* (Dec. 23, 2024), discusses psychedelics and the blurring of lines between medical, recreational, and religious use. I guarantee that likely every one of you has at least a patient who has used psychedelics, knows someone who has, or will have questions about them. Some of you may have already used them. This is a field in medicine you will have to know about because there are drug interactions, and people will come in with serotonin syndrome. Plus, your patients will ask about it—what do we do when the things that are not working for us? It will raise questions for you. It is an important topic.

What are psychedelics? They have been around for a long time, and there are natural and synthetic ones. Some natural ones: there is a toad, and there is a drug called DMT that comes from the toad. We are doing research with it currently in treatment-resistant depression. It is an inhaled product being developed by Beckley Psytech, a company out of England, and it is in Phase III studies right now. The second picture is of mushrooms, where psilocybin comes from. There are many studies going on with psilocybin currently. There are two Phase III trials for depression; there are studies going on for OCD, and we will go over some of that data. Those are some naturally occurring molecules.

There are classical psychedelics, generally thought to be the ones that work through the 5-HT receptors. Not to get into simple semantics, but psychedelics can be synthetic or naturally occurring. We talked about psilocybin, which is naturally occurring, but LSD has been around a long time and is synthetic. There are other drugs, like MDMA and ketamine, which are also psychedelics, but they are not classic psychedelics because they do not work through that receptor—they work through the NMDA receptor and others. But why are they lumped in? Subjectively, chronologically, they cause a similar experience; they cause patients to go into an altered state and have a very deeply subjective experience. So they get lumped together under the category of psychedelics. Psychedelic 5-HT receptors are synthetic, and there are naturally occurring ones, and then there are other drugs that do not work that receptor but have a similar response when you see it in the clinic.

How do they work? This is something that I think a lot about. We will touch back on this later. There are many ways to explain how they work, and yet I do not think any of them fully explain it because I do not know that we fully understand it. For this slide, the left is a schematic, a functional MRI of the brain. On the left is a brain not on psilocybin, and the one on the right is on psilocybin. What you see is that there are more connections made between different lobes of the brain that were not previously there. The temporal lobe and the frontal lobe start making connections that were not previously observed. Those are the MRIs that were done in patients. They received psilocybin, they went through MRIs, and this is what we found. Another way to think about it, besides the receptor, the MRI, is what happens in the brain. It is thought to maybe work in something called a default mode network. What is that? That is the part of your brain that is always looking for problems. It is vigilant. You are always scanning—some of us more than others, depending on your history—you are always looking for problems. That part of the brain in the amygdala seems to quiet down, and then other parts of the brain seem to wake up—the temporal lobe and start to make connections, and people are able to get insights because they are not in this sort of fear response. That is another way to think about it. I will tell you some stories about what patients report when they are on it because I do not think any of these are adequate to fully describe what is happening. Where does the word psychedelic come from? It is from a psychiatrist named Humphry Osmond in 1956 and literally means "mind manifesting." Psycho means manifest your mind, the amplifier of your mind. It is pretty interesting. A little bit of history.

Psychedelics did not just appear today. They have been around for a long time—thousands of years. In the US, much research was done in the 50s and 70s. This gentleman, Gordon Wasson, went down to Mexico and underwent a psilocybin ceremony with Maria Sabina, the woman you see there. He came back and talked about it. Albert Hofmann synthesized psilocybin—the extracted medium in mushrooms—and then Sandoz started making it. Before prohibition, you could write to Sandoz, and they would mail you LSD, and then you would start doing experiments with it. From the 50s to the 60s, more than a thousand papers were published, with almost 40,000 patients and many books and papers. At that time, they were thought to be tools that could be used to understand how the brain works, underlying psychedelic processes. But really, that research would not be considered rigorous by current scientific standards. A lot of that was anecdotal evidence; there were not good assessment features, not a lot of follow-up. The statistics would not be what we consider modern, and there were not a lot of control groups. Even though a lot of people were treated, I would say the research was not as rigorous as what we would consider today.

What did some of that research before prohibition find? It induced a phenomenology that had biological, psychological, and spiritual dimensions. It generated all of these findings. People found it to be dose-dependent, so the higher the dose, the bigger the experience. There were sensory distortions, really intensification of affects. If you were sad, you would really start crying intensely; fear, everything got intensified. The meaning-making capacities also appear to intensify. People have these subjective experiences and make meaning out of them. This is a key point that I will pull on throughout the talk. It seemed to be dependent on non-pharmacologic things. That is really unusual in medicine. If you give an aspirin, it does not matter about the other factors or other antibiotics, but psychedelics seem to be really impacted by who is giving them and in what context. That was an important finding that was starting to emerge. This is where it gets into a therapist's role. There is a clinician who needs to be alongside the person when they are getting a psychedelic. It is important for them to have a sense of safety. That does not really happen that much in

medicine. You want your surgeon to be nice, but as long as they take your gall bladder, it does not matter all that much. Here, it seems to matter a whole lot.

Some of the early studies showed they were not helpful with schizophrenic patients. In fact, they worsened their symptoms, but other neurologic disorders seemed to help anxiety, depression, and OCD. They treated alcoholism with it. There were published studies in the 60s along those lines. But again, there were methodologic challenges—inconsistent treatment application, lack of control groups, and subjective outcome measures. Despite these flaws, evidence suggested psychedelics had a treatment for treating these non-psychotic disorders, and more researchers were needed. What happened? It all came to an end. At that time in the 60s, the counterculture movement overlapped with those in equal rights opposition to the Vietnam War. Greater tensions came to the government, and so they began burning draft cards with public protests. In '66, the Senate had hearings with a goal of stopping psychedelic use, making them illegal. This was an important act that was passed in 1970—the Comprehensive Drug Abuse Prevention and Control Act. Psychedelics, which were widely used and researched, became Schedule I, which means that all research was immediately stopped. Schedule I substances were described as having a high potential for abuse, no accepted medical use, and so pretty much all research—everything that was happening in the 40s, 50s, and 60s—stopped at that time. This graph shows you that. These were the papers being published before scheduling, and then you can see 1970, that dark line, and then all the papers drop off.

Then, you can see again in 2001, it started going up, and then now from 2017 on, you can see the slope going up. There are literally tons and tons of papers now being published. That is why you are seeing it so much more in the news today, and that is why I am here speaking with you. How does this all start? In the early 2000s, a bunch of researchers said, these chronic problems that we have had with depression and anxiety and alcoholism, we seem to be running out against roadblocks. We are just making so much progress with death anxiety from cancer. They were able to convince the FDA to start reinitiating this type of research. One of the first ones happened with Roland Griffiths at Johns Hopkins. At that time, most of the funding was from private donors, but this led to a wide stream of research that is quite exciting, and we will go through some of that research now and coverage of these studies that started to legitimize these substances.

This is modern psychedelic research. We will go into a little more detail about some of the bigger studies in depression and trauma, but there are studies being done in OCD, bipolar disorder, anorexia, alcohol and smoking cessation, chronic pain, and cluster headaches. It is a broad range. There is a rheumatologist at UCLA starting to do studies there. It is really in a wide range of fields, and I think it is an emerging specialty that is not yet established. People in psychiatry are studying it, as are people in neurology. Cancer centers, such as Dana Farber, have opened their psychedelic centers, and Ohio State Cancer Center has opened theirs. Oncologists are involved. It is a mix of many different fields, and I suspect in a few years there will actually be a subspecialty of psychedelic medicine. Where it falls in training, we do not yet know, but it is an emerging field.

Let's see here. Some of the modern psychedelic research: we will dive into a couple of these studies a little bit more, but to give you a sense, there were a couple of studies published in the *New England Journal of Medicine*, one in 2022, that treated 233 patients with psilocybin versus placebo for treatment-resistant depression. That is a significant group of people that you probably do not see a

lot of. You will refer those out to psychiatrists. Generally, they fail two to five treatments of antidepressants. They are really refractory to any medications and probably have had anti-depression treatment for 10 to 20 years. Twenty-six percent of them went into remission after one dose. Robin Carr published something in the *New England Journal* a few years earlier; they compared it to Lexapro. Again, they found that 3% of them went into remission. The other big drug that has gotten a lot of press and many studies is MDMA for trauma. Sixty-seven percent of the patients no longer qualified for trauma after three sessions of MDMA. These were people with complex trauma, military veterans, sexual abuse, really severe refractory trauma.

We will go into a little bit more detail about this, but these are current studies. This is the psilocybin study that I mentioned with 233 patients. The blue line is a 25-milligram dose, and the top line is a 1-milligram dose, which counted as placebo. I am happy to send these publications to you to look into it more deeply. Again, 29% went for a mission versus 8% with the 1-milligram dose. Chuck Rizan published a study in *JAMA* just two years ago. This was MDD, major depressive disorder, rather than treatment-resistant disorder; this was just major depression. They treated 104 patients, 25 milligrams with a placebo. The FDA either wants you to use niacin or a low-dose psychedelic as your placebo. He used niacin, and it causes flushing, trying to mimic a psychedelic. Again, it shows a dramatic response. What they use to measure this is something called a MADRS score. I will talk more about this later, but it is not like blood pressure or hematocrit, which you can just measure.

How do you assess if someone's depression is better or not? We use something called a MADRS, which is a clinician-administered test. An independent rater is called, and they give you a scale and points, and that is how you determine if you are depressed or not, and then how many points that change determines depression severity and how much you responded. You can see that these patients responded with almost 20 points, which leads them into a remission, in a sense not having depression anymore. People who were not as depressed seem to do better, which makes sense. Forty-four percent went into remission versus 11%. Remission has a specific meaning in psychiatric terms. Response is that your depression has improved. Remission is when your depression actually went back down to normal, so you were no longer depressed, which is really quite unusual. You have a dose of this, you are no longer depressed, and then you come off of it. It is just a one-time dose. It is not an ongoing treatment. The remission difference is placebo versus the active drug, and all of them used psilocybin. Just giving you a range of 20s to 40s. I will go through some of these a little faster now. I should mention this: there are two studies that are in Phase III trials now, one with Compass Pathways and one with Usona, both for depression. The Usona study will probably finish in the middle of this year; the data will get locked and get submitted to the FDA probably by the end of the year or next year for approval. Compass Pathways is probably on a similar timeline. There is a very good chance that there will be an approved psychedelic for the treatment of depression sometime next year, and you will have to know whom to refer your patients to, why, who is the right person—all those things will need to get worked out. That is how far along these studies are now.

This is the MDMA PTSD study, and CAPS-5 is on the left. That is like the MADRS, except it measures trauma. We treated a fair number of people, not on this specific study, but a very similar study. As an oncologist, I had never seen something that created such a shift. You think of oncology and patients, and it really causes a lot of existential distress. You lose meaning, you lose control of your life. People with PTSD look and seem normal, and you would not know how much trauma they feel, but it

is actually quite debilitating. It was remarkable to see people able to go back to work and be functional again through this study. This is building on that. It is also used a lot for substance use: for tobacco, UCLA is doing one on cocaine. Opioids—it is being used in multiple sites for that; alcohol use disorder, and we will touch on a couple of those. This was a study done at Hopkins, and it is just finishing; in fact, it is not published yet. It is a randomized smokers trial of psilocybin versus nicotine patches. It was quite a heavy smoking group. They smoked about a pack a day for almost 26 years and had tried to quit seven times. The middle chart is what the Hopkins study was. You can see their abstinence continuing to improve after one dose of psilocybin, whereas the nicotine patch continues to decrease. I want to pause for a second because I have told you about the drug, you give it, and what is going on. Why does this happen? They did narrative interviews of some of these patients. Why did you stop smoking? I point to this because I want to come back to that. The patients reported, and they said the most banal things, like, "When I was on psilocybin and I was under the music, I realized I was harming myself. I was killing myself." They had this deeply subjective experience that they were harming themselves, not just a mental one, but an experiential one. They have been told that it causes cancer and heart disease; you should stop smoking. Yet something, some sort of subjective effect that they had, makes them realize that and want to stop. That is an important point, and we will come back to that. This was published in *JAMA Psychiatry*, by Bogenschutz, using psilocybin for alcohol use disorder. Pretty heavy drinkers, and again, a similar theme. This was published in *JAMA Psychiatry* last year, showing a diminishment in that. It is also being used for many other things: anorexia, PTSD, OCD, and chronic pain.

The OCD study is also a similar story to that one. We did not do that study, but I was talking to one of the investigators, and I said, "What is going on there? Why is the OCD improved?" One of the therapists described that this woman, she had very, she was very controlling, and so she had everything sort of rigid in place externally, like furniture, but also internally, a very rigid structure. She reported that her mother was very critical of her when she was young, and so she developed this personality and needed everything to be in place. While she was on the psilocybin with her therapists, she became sort of playful, and they started rearranging the furniture. That became a source of creativity, rather than this thing that had to be rigid in place. She was able, with the support of her therapist, to be creative with that, and they were unlocking her own internal rigidity, allowing her OCD symptoms to diminish. She just felt this ease, felt compassion for herself, knowing what major rigid reflected on her mother's influence on her, which allowed the subjective experience to improve some of her OCD symptoms. It has gone from hippie culture to major science. There is federal funding going on. You will see a lot more funding coming out of the NIH for these disorders. The NCI has a study for psilocybin in advanced cancer. The NIH had one for ALS, and you will see an increasing amount of federal funding going on. The VA has just launched multiple studies now to treat vets with PTSD using psychedelics. We just applied for a grant from the DOD to treat TBI for veterans. It is really going from philanthropic to federal funding.

Okay, that was history—old research, new research—and a little bit about me and why I am here. This is where I work, at the Aquilino Cancer Center. I am an oncologist, and how did an oncologist from Georgetown end up doing psychedelic research? It is a long story, but the shorter story is I came here, as you heard, to do philosophy. I wanted to be a philosopher when I was an undergrad, but my dad said, "I did not come to this country for you to be a philosopher." As a good Indian, I went to medical school and became a doctor, but then Georgetown had this philosophy degree. So I came here and did internal medicine, and then I went into practice and research in oncology. I was at the

NCI and did ethics research there as well as Phase I drug trials. Then I went into practice. After about 18 years or so, seeing a lot of patients—I think I did over a hundred thousand patient encounters—I started feeling burned out and lost some connection with my work. What dawned on me was that a lot of oncology focused on things above the water—surgery, radiation, chemotherapy—but really, people's quality of life, we did not do a lot with that, which is a lot of things underneath the water—what we call integrated oncology or psycho-oncology or psychospiritual issues. Really, we were not trained much in that. Nobody talked about it. At the NCI, you give people bad news, but you never really went beyond that. I did a lot of that in my practice, but I could only go so far, and that is when I learned about psychedelic research and then went and did a fellowship to learn more about it and then set up—you have to figure this out—because they purported to address what we call existential distress in cancer patients.

How in the world do these drugs address something like this? It just seemed crazy to me. I wrote a study and I went to my partners and said, "I want to study psychedelics." With an NCI degree and a philosophy degree, this was fine as long as it cleared the FDA. We built out this healing space that you are seeing here at the Cancer Center; that is what it looks like, where we could study psychedelics. Over the last 18 months, we have delivered roughly 250 treatments. We are doing a wide array of studies, using different drugs from MDMA to psilocybin to 5-MeO, which are ones that you may not know about, or you want to force a synthetic drug that is shorter acting than psilocybin. If I showed you that list, there are probably 400 new psychedelics in the pipeline being developed, for lots of different indications from depression to anxiety to PTSD, to cancer-related anxiety, and postpartum depression.

That is a little bit about why I got into this, but I want to talk a little bit about the treatment itself. This is a new paradigm. You would not normally know this, but this is not like other parts of medicine. It is not like psychiatry, where you give someone a medication. It is not like therapy, where you talk to them for an hour. It is not like internal medicine, where you go and see a patient, examine them, and then they go on after 15 minutes. Is it probably closest to surgery, with a pre-op, operation and post-op. It is also different and it is not just the drug, as I hinted at. It is the drug plus the setting. There are three factors: one is the drug—the type, quality, and how much of the drug is taken—but also where, how, and to whom the dosing is being given. Who the person is in the room and who is administering the drug actually matters. Then there is the mindset of the person going in. We spend a lot of time preparing the mindset of the person going in for the treatment. One of the keys is safety. Unless the person feels really safe, they are not able to go deep into their psyche, so how do you establish that safety? It matters more in this than probably any other field in medicine that I have seen. It is a new paradigm, and I will come back to this later because the FDA is really struggling with how to regulate this.

The FDA knows how to regulate a drug, but how do you regulate therapy? It would be like if you are going into percutaneous coronary intervention, but along with how you did it, they also wanted to regulate—what you said, how you did it. How do they figure out what is allowed and not allowed to do? It is a new paradigm; more of the experience is being regulated, not just the medicine, and that is quite different for anything in medicine. It is just not something the FDA has had to deal with. It is something that physicians will have to figure out. If somebody is referred to a study, there is a fairly thorough assessment to say if it is safe for them, or if there are things about their history, psychological and medical, that makes them not safe. Sometimes we have to take them off

medications. Then there is a preparation phase, then there is the dosing, and then there is the integration. That is like pre-op, operation, post-op. This is the individual operation. Usually, there are two or three sessions, sometimes four, where they meet a therapist or the provider and talk to them about why they are doing this, about their past, what to expect, what could come up for them, really helping them navigate that. The dosing session is eight hours. They come into a room with eye shades and music, and they are lying down with one or two therapists for the entire time. Once they are finished and they are safe to go home, they are discharged, and then they come back the next day and several more times to do what is called integration—post-op here—to see what happened, what came up, how can you make sense of it? How can that impact your life? If you think about it, there is not really anything like that in medicine that we do.

This is a new modality of treatment, and centers are having to be built, space having to be created, and how to do this, and schedules are quite different for this. There are a lot of operational as well as practical challenges in this. Going back, I wanted to study this, and this is a study that I designed. It was group therapy. We gave four cancer patients at a time psilocybin to assess how they did. The day before, there would be group preparation, then they would get psilocybin, and the next day they would come back and talk about it a week later, and then we would assess it eight weeks later to see how they did with psilocybin. We published this in *JAMA Oncology* two years ago.

This is again the MADRS I had mentioned. The MADRS is a measure of depression, HAM is one for anxiety. Both are clinician-administered, and the QIDS is a self-reported depression scale. You are all familiar with these measures. Eighty percent of the people had a 50% reduction of their depression symptoms. Fifty percent went into remission. When I saw this, it made me end up leaving oncology to do this research full time because I found it so compelling. This is the 18-month follow-up of the same patient population, and this is under review in *Cancer* and hopefully will come out sometime this year, but 18 months later, people continue to be in remission from their depression symptoms. Generally, it is well-tolerated. Some headaches, mood changes, and fatigue, but it is quite intense treatment. No significant adverse events.

Partly from seeing the results from the things, but what did we see phenomenologically? What were patients reporting? What was happening? To give you a little taste of that, this was one of my patients with metastatic kidney cancer who was on the study. She had psilocybin. It was a really intense treatment, and she said she was really struggling with death. She literally felt like she was dying in the psilocybin session, and it was intense. Then she came out of it, talked the next day, and then a week later when I saw her, she reported that she was at a lake, and it was evening in the fall, and she heard these crickets, and they were really loud. It got really, really loud, and then she had a sense of peace that came over her. What she realized was either crickets are, and come winter, they are all going to die, and come spring, there are going to be a whole lot of new crickets. She said, "When I was born, there were all these humans, and throughout my life, they died and new ones were born." For her, it became this very personal thing: it is not personal that I am dying. I am part of life that comes and goes. I could tell her this. She has read this. She knows that everyone dies, but on some experiential, meaning-making level, she was able to internalize that, and that gave her, not that she wanted to die, but it allowed her to see a part of a larger context about her illness. People talk about the increased sensory input, distorted sense of time. It is the most deeply subjective experience that I have ever seen people experience. People really report that they are most

themselves, they just feel themselves, and I have not seen anything like that in medicine. Now going to the FDA.

The FDA, and where we are right now, gave landmark guidance in 2023. It was the first time the FDA really weighed in on this topic. It targeted scientists and researchers and helped guide how to get this into the FDA. One of the things that they really struggled with was psychological support. When these drugs are approved, you will not just be able to prescribe them. You will have to have a certain license, but then it is not that you take psilocybin and go home. You will be coming into a center, and then at the center, you will have at least one, currently two therapists who have to be with you when you are on it. It is unclear what the qualifications should be for those therapists. Should it be master's or PhD level, or should it be an MD or PhD? What is the right training that is required for it? What type of therapy is right? Is it interventional? How do you pair it? How do you regulate it? The FDA is really struggling with this, and they talk about that.

There are lots of challenges for psychedelic research. One of the ones I really want to focus on is that there is a lack of good biomarkers for mental health and for psychiatry. What do I mean by that? There is this inherent tension between objectivity and subjectivity. What do I mean? Like your blood pressure, I can measure that. Your tumor size, I can measure that. But how do I measure the state of someone's mind? I do not have a CAT scan to give you to figure out whether you have depression or trauma. Mostly you report your symptoms, you feel anguish, you put a label on it, and then we have certain diagnostic criteria, and I interpret that and try to give you that. But does that really capture what is going on inside of someone's mind? It is really subjective, and we do not have a good measure for that. These sessions are very intense. They are very subjective. They last a long time, and how do we know what exactly is happening? How do we capture that? It gets to this notion of what is the value of the subjective experience? Is it only what we can measure versus what you feel is subjective wood? How do we resolve that? One of the things that we see is people start making new narratives about their own lives. They see their mental health, they see their mental health struggles diagnosed as something separate from who they are. They are not just their depression. These are all internal subjective feelings. They are not external things you necessarily measure. They feel like they can author their own life. This tension between what to do with subjective information, how to think about it versus objective information is not new to psychiatry or psychedelics. It has been long debated by philosophers of mind and science.

One of my favorite classes when I was taking philosophers was an epistemology class. I will talk about one of my favorite books, “The Structure of Scientific Revolutions” by Thomas Kuhn. There is something in epistemology called the "hard problem of consciousness." Where does consciousness reside? It is a challenge to explain how and why objective experience arises from physical processes in the brain. It contrasts with the easy problems of consciousness, like perception, memory, and behavior. We are studying those, but what does it feel like to be something? What does it feel like to be human, which is different than red or a memory? What is the core tension? Objective science seeks universal truths and finds measurable data. Subjective experience is deeply personal and qualitative and resistant to generalization. The entire group of people, reductionists, objectivists—can a scientific objective framework ever fully account for the richness and personal meaning of a subjective experience? Reductionists would say yes, and critics would say no. They say that the subjective experience is something that cannot be reduced. They say subjectivity is not a weakness, but a source of insight and value.

If I go back now to how these drugs work, it felt normal to say, well, they hit this receptor, they did this in the brain. Is that fully captured what happened, or were the stories that I told you important in terms of what actually happened? When I told you about the patient who smoked and decided it was killing him, or the cancer patient that I told you about, or the woman with OCD, it was her personal meaning of what she made that was really fundamentally what changed what she did. None of these things are captured by these objective measures. How do we reconcile that? That is something I have really been struggling with doing this research. We present the data, we present how the depression scores improved, we present MRIs, but then it is the intensely subjective experience that changes people. How do we report and talk about that? How do I reduce that down into something that makes sense in medicine? There is a quote that I found with Einstein that speaks to me: "Not everything that can be counted counts, and not everything that counts can be counted." There is a real tension in that for me. It is not that we should not measure, but not everything that is measured is able to capture what is really important.

To go one step further, how does this connect with clinical care? It has to do with meaning. How does meaning relate to this debate? Science often avoids discussing meaning because it is subjective and not measurable. We talk about when neurons fire, whereas critics argue that meaning is central to the human experience. It arises from personal experiences, and science cannot account for it. Reductionists would argue that you can talk about neurochemical processes. The meaning of love is reduced to oxytocin and dopamine, whereas subjectivists would say it misses the real reality of meaning. What it feels like to be in love or to find purpose cannot be captured by describing brain states. This tension between objectivity and subjectivity is something that I am really grappling with and trying to sort out. How do we talk about it in medicine, and what implication does that have for us? How does this come back to what I was talking about? What we do in oncology, a lot of the focus is on what is above the water. What is the treatment? How do I shrink the tumor? It is all objective. How people experience their illness and how they think about themselves is all subjective.

I find it very frustrating as an oncologist to walk out of rooms and leave families devastated with a diagnosis but not having great tools for that, even though you are shrinking the tumor, you are not addressing that subjective piece. This is how this objective-subjective debate bleeds into clinical care. Part of it is to know that you are working from a paradigm. We are not going to resolve this debate today, and I do not have a new resolution for it. It is not that subjective is less important or objective is more, but that you are living with a dominant view that there is an objective view that is regarded to be more dominant in medicine. We tend to think of the patient on six blasts with heart failure. What the ejection fraction is, is probably more important than we think about his personal story in treating his heart failure. What are the personal things about that person? What do they matter? Does it really matter in taking care of that person? Whether you know it or not, somewhere we have internalized the importance of the objective and diminished the subjective part of it. That ends up affecting patient care in ways that we will talk about.

I think that we are in a paradigm shift in some ways. Thomas Kuhn, who I mentioned earlier, wrote “The Structure of Scientific Revolutions.” He is a philosopher and a physicist, and he studied physics. He talked about the Copernican view, the Galilean view, how we went from a flat world to a round world. He studied how those things occurred. He coined the term "paradigm shift." He found that generally we are living in a paradigm, and we have all this data that supports it, and then you start getting some data that falls outside of it, and you ignore it and you ignore it, but then you get more

and more data. All of a sudden, one day you just shift, and then you have this new paradigm. It is not this gradual incremental thing. It is like you believe, believe, believe, you ignore, ignore, ignore, and all of a sudden, it becomes so dominant, it just shifts. Actually, that view comes from the people who were in this field who got frustrated with it and then started generating this data.

The transition from a paradigm to a new one is far from a cumulative process. Once a transition is complete, the profession will have changed its view of the field, its methods, its goals, much like picking up the other end of the stick, a process that involves handling the same bundle of data as before, but placing them in a new system of relations with one another by giving them a different framework. In a way, you could see that is what people are doing in these experiences. Nothing is fundamentally changing about their life—the cancer diagnosis, their past, their traumas—and yet they are able to think about them in a different way, and all of a sudden, it changes how they are. Similarly in the field, I think medicine is going through a paradigm shift. Antibiotics and anesthesia changed medicine tremendously. They took us from shamans to releasing objective data as being very powerful, and we are probably running into the limits of how far that can go while neglecting the subjective. How does that come in? Right now I have seen more physicians burned out than I have ever seen. Patients are not happy with their medical care. They feel like they are just obstacles moving through frequently. People paying for medicine think it is really expensive. Something is not working in the system. Is a paradigm shift coming? This is another way to say that: All truth passes through three stages. First, it is ridiculed; second, it is violently opposed; third, it is accepted as self-evident. That is what paradigm shifts can be like.

What are bedside implications? This is one of my favorite quotes from Jung: “Know all the theories, master all the techniques, but as you touch a human soul, there will be another human soul.” That is where I will come to in many places in terms of probably the time that I knew the most, when I was finishing residency here. Since that time, it has been an unraveling of what I really thought I knew. After my fellowships, my philosophy degree, my research degree, my time at the NCI, and treating all these people, at the end of the day, sitting with another person, soul to soul, I challenge you that as you are busy with the morning report and attendings and what fellowship you will get into and all the things you want to achieve, maybe once a week or twice a week when you have done the task that you got to do, if you sit with another person, human to human, soul to soul, and let them know that you see them, that they are not just their disease, that there is a human behind that. That requires subjectivity. How will you know that you did it? You will feel more enlivened. You will feel like, "Oh, this is not a burden to do." You will feel this connection. That is actually a feeling of meaning, and that is what I have had to rediscover through this work.

Meaning itself is an intrinsic reward, more than the accolades and the financial rewards. Over time in your career, you will find that it can sustain you more than the external accomplishments. You do not have to do it all the time, but see if you can connect, and you have to do it your own way, in your own style. How can you really connect with that person from soul to soul? Let us see that.

Where are psychedelics going? There is still a lot of stigma to overcome because they are misunderstood. I find people who overhype them; they think they are the magic bullet and cure everything, or they are really scared about their side effects. Neither one of them are true. Understanding the subjective experience, which we have talked a lot about, identifying

acknowledgeable risks, setting expectations, and then outlining the therapy and best practice and therapist training, that is the way forward. Thank you.

Q&A

When looking at the studies that are currently being done, is the administration of the psilocybin and the pre- and post- similar across studies, so that there is some ability to compare the outcomes? If the mechanism of delivery and follow-up and preparation is so different, how much impact is that? Is there some standardization? I know you talked about that being developed, but in the current studies?
That is a really good point. There is not a standardization, and that is one of the places of controversy. This is a game that is being played right now. The FDA does not know how to regulate that. Drug companies sometimes are minimizing the pre-op and post-op because the FDA does not know how to think about it. There is not yet a clear standard of what that looks like. Everyone needs to know what happens, but they are minimizing it. The FDA does not look at it too closely. There are different approaches, different thoughts. I have a slide that highlights the pharma partners and the number of required hours of training–some have more, some less some. We just completed a study where one of the companies had a minimal amount of support, and the patient complained, "If I could figure out this trauma on my own, I would have. I wish I had more support." It is still early days.

Has anyone designed a study where you take the same dose, say, psilocybin 25, and you assign people to either a really good environment, a mediocre environment, or a terrible environment, and then just compare the outcome of the environment? Would that be an ethical design?

That is exactly what the FDA has asked one of the companies for. They said, "How do we know what is not the environment that is really doing it?" They asked, "Can you give this drug without a placebo? This shows there is an effect." They want to know about the environment—how much of it is drug, how much is the environment? How do you get at that? People are designing that, and there is a debate in the field. Is it ethical to give someone with anguish an altered state without a lot of support? That is why I think there are starting to be those studies being designed. I guess the question I have along those lines is, how much is the facilitator manipulating the endpoint? What is scary about these is the potential for them to be used in a non-safe space, a negative environment. Are there stories, maybe not data, but stories of people coming out with a worse outcome or negative time? In controlled environments, there are not so many of those. People are suggestible, and that is why things can go sideways. That is why the FDA is concerned. This is quite different from other modes of therapy where the therapist is not supposed to go in and say, "Think about your mother or go deal with this problem." You trust whatever comes up for the person is what is coming up, and then you help them deal with it. It is really quite subtle. People have these emotional states, and what the therapist is doing is providing a corrective experience. If they had distress from some childhood experience in another time, the therapist does not intervene but is supposed to provide support for them to do that.

If the therapist or person is not good, and they are too interventionalist, it could do some harm?

That is absolutely right. This is why training is a huge piece of this. Our therapists have to go through didactic training, and they get supervisioned. All of our sessions are videoed and recorded, and then the senior therapist reviews them and goes over that. That is absolutely a concern. Thank you so much for the presentation. Since it is such a subjective and a reflexive experience, I think you were kind of talking about it before, but have there been, like, a worsening of mental experience after the sessions? Depending on what is going on, a lot of times with people with trauma and certainly severe depression, there can be transient worsening. One of the mechanisms that we think is happening is that you may have had a very difficult experience, and in your mind, you sort of blocked it off, but it is still there, and the mind wants to be whole. Part of that is integrating that experience back into it, so while you are going to that integrationing, a lot of times people get worse before they get better. The grief that you did not want to feel, or the fear, or the anguish, is sort of low-lying there. It is influencing your behavior and causing symptoms, but you have sort of kept it in the closet, and then the closet is opened. Then there is a process of integrating that, and that can be a worsening of symptoms, and you need a lot of support through that.

Since MDMA stimulates the brain of oxytocin secretion, would there be a role for combining MDMA with other therapies acting on different brain pathways, similar to targeting different pathways in other diseases that we treat?

For sure. That is where I think the next phase of work is going to be. There are talks of combining MDMA and psilocybin, but MDMA and other types of therapies. One of the things I want to say is that in the early days, the specialty is just getting established. Where does this fall? Does it fall in neurology or psychiatry or medicine? These are the questions that will be the next phase.

I have been trying to refer people to these types of treatments, but access is challenging. The hope is that there will be more availability. Is there availability in the Washington, D.C., area?

Our company or organization is called Sunstone Therapy. We have eight studies going on right now. If you go to our website, you can always refer patients there. Johns Hopkins is doing studies, and Shepherd Pratt is doing studies. We have the most extensive number of studies locally. We are the only center in the DMV that is doing any studies, but we are happy to see people, and we treat people every day.