Quick Takes
A PODCAST BY PHYSICIANS FOR PHYSICIANS
HOSTED BY DR. DAVID GRATZER

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Psilocybin in the treatment of depression with Dr. Ishrat Husain

[Musical intro]

David Gratzer: *In the 1960s magic mushrooms, or psilocybin to use the scientific name, was of interest because of possible treatment for mental illnesses. Jump ahead a few decades and there's renewed enthusiasm, including excited headlines in the press and very active research, including a major new paper published in the* New England Journal of Medicine*. So, is psilocybin living up to the hype? Is this a possible breakthrough in the treatment of refractory depression? And what's next? The return of bell bottoms?*

I'm Dr. David Gratzer. Welcome to *Quick Takes* and today's guest, Dr. Ishrat Husain. Dr. Husain is lead of the Mood Disorder Service here at the Centre for Addiction and Mental Health, where he's also head of the Clinical Trials Unit. He is a Tier 2 Canada Research Chair in Treatment, Innovation and Mood Disorders, and he's an associate professor of psychiatry at the University of Toronto. Oh, and did I mention he's the co-author of that major new *New England Journal of Medicine* paper? Welcome, Dr. Husain.

Ishrat Husain: Thank you for having me here, Dr. Gratzer.

David Gratzer: Sir, what to make of all of the excitement around psilocybin?

Ishrat Husain: I think it's encouraging that there's such a focus on new ways to treat the most common mental health condition that's afflicting society. I really encourage inquiries into new lines of research, and it's really encouraging that there is now also funding to support investigation of new treatments for refractory depression, which is a highly disabling condition. So on one hand, the excitement is encouraged. On the other hand, we have to be cautiously optimistic as well about some of the data that's coming, because by no means is it confirmed that psilocybin is now ready for us to use in our clinics.

David Gratzer: You're cautious.

Ishrat Husain: I'm cautious - and optimistic!

David Gratzer: Fair enough. The media reports have been very encouraging. What are your thoughts on that?

Ishrat Husain: I think that the media reports sometimes are in danger of putting the cart before the horse. I think creating such hype and excitement means that the public that is receiving some of this news is eager for access to this new treatment approach, so much so that they may begin to start looking into ways that they can access it themselves without medical oversight or supervision. So, I think that it's a fine line, and I think that it's really important for us as a body of physicians and professionals that we are educated and are critically appraising the literature that's coming out so that we can have those discussions with our patients and the public.

David Gratzer: We'll talk about the literature in a moment. But when there are many positive headlines and media reports, when there's chatter on social media, that's so encouraging, inevitably, patients ask us and the last time somebody asked me about psilocybin was, I don't know, a couple of days ago. What sort of response do you give to a patient or a family member of a patient who asks about the potential of psilocybin for somebody who's struggling with depression?

Ishrat Husain: So my general answer is to tell patients that psilocybin is still very much an experimental treatment. There's been so much interest from patients and the public that I, together with colleagues at CANMAT published a consensus statement in the *Canadian Journal of Psychiatry* summarising essentially what I tell patients day-to-day, which is that psilocybin, although it has encouraging data on its safety and efficacy for depression, is still very much an experimental treatment that really should be exclusively accessed through clinical trials or in very rare special circumstances through the Health Canada Special Access Programme. So that is my approach when the public and patients ask me about it.

David Gratzer: And thinking about the literature, what do you see?

Ishrat Husain: What I see in the literature initially is a very strong, positive effect sizes for an antidepressant, effect for psilocybin. I see very few incidents of serious adverse events if you pool together the data from all published clinical trials in major depression. But I also see lots of limitations in the published studies thus far. These range from small sample sizes to lack of adequate control groups to homogenous samples recruited to these studies to short follow-up periods. So, I feel that the data is very much encouraging, but until some of the limitations are at least in part addressed, I think that we need to again be cautious before we say that this is now a transformational treatment in the management of refractory depression.

David Gratzer: The big paper is the Goodwin paper. There have been other papers. There's a lot to like about Goodwin. Start here: 233 enrolled, randomised controlled trial, *New England Journal of Medicine* (there's your brand name recognition) and we've got a pretty robust result. How would you summarise those results?

Ishrat Husain: Yeah, so it's a three-arm study. They used a one milligram dose of psilocybin as effectively an active control. I was a part of the team that, led the study. We led the Canadian site at CAMH and we randomised patients to receive either 25 milligrams of psilocybin which is in almost 100% of cases likely to induce a psychedelic experience that lasts up to 6 to 8 hours. And then the second arm in the study was a what's considered a medium dose of psilocybin ten milligrams, which would cause milder psychoactive or psychedelic effects in most individuals. And then, as I mentioned, the one milligram active placebo. The results were encouraging in that it showed that the psychedelic dose, the 25-milligram dose, was superior than smaller doses in reducing symptoms of depression, as measured by the MADRS, which is a clinician rated measure of depression. The results also showed that 40% almost of people in the 25-milligram dose arm had an antidepressant response. And that up to a third were in remission at the primary time point, which was three weeks after the psilocybin administration. So those are all very encouraging findings. But also, there were some adverse effects as well in all three groups. And that's something that we need to be aware of as well and appreciate that, you know, it's not necessarily all sunshine and rainbows.

David Gratzer: In fact, 84% of people in the 25-milligram group had an adverse response ranging from dizziness to headache, right. I mean, the MADRS drop was significant. So in the 25-milligram group is 12 points as opposed to that, which is significant. There are some practical things that come up, though, that temper enthusiasm. So that runs in the *New England Journal of Medicine*. But it runs with an editorial by Madras, no connection to the scale she's got two A's in her name, and she talks about some of the practical issues around use of psilocybin. What are your thoughts on some of these practical issues?

Ishrat Husain: I have lots of thoughts on how, if, and when psilocybin is shown to be effective and safe, how it would be implemented pragmatically in an already strained health care service. You have to remember that in all of these clinical trials, psilocybin is delivered with quite a large amount of attentive and relatively intense psychological support from trained therapists. So, in the Compass study, the one study published in the *New England Journal of Medicine* that you're referring to, the amount of psychotherapy for each participant amounted to almost 12 hours, which is a lot, and may be actually confounding the antidepressant effects that we're seeing. So practically, I just often wonder, as somebody working in frontline psychiatry as well as is, how would we implement something like this into our current treatment algorithms and how would we actually scale it up? So that's all my questions about the practicality of it. Also, these are studies that have highly selected groups of individuals, no personal or family history of any psychotic illness, no other psychiatric comorbidity that we didn't recruit people with suicidal ideation – and we know that lots of people with depression experience suicidal ideation. We know lots of people with depression have co-morbidities. So, you know, the findings of this study may not be generalisable to all people with depression.

David Gratzer: What are some unanswered questions that you think we need to answer?

Ishrat Husain: So, one thing that I'm curious about scientifically is whether the subjective psychedelic experience, the "trip" as it's so called, is whether that's the key element or active ingredient of a therapeutic effect. It's a very complex intervention if you think about it. It really does combine the biological, psychological, spiritual model of mental illness because you have a biological approach and that you're delivering a medicine, you're getting psychological support to patients by giving them preparation, support during the treatment and then integration afterwards. And then you've got this subjective experience, which is quite spiritual for a lot of people. It's called the mystical experience for some. So how we tease each of those apart to see what is the key ingredient is something that I'm fascinated by. I mean, we may find that it's just a combination. They all convalesce to come together and lead to this antidepressant response. We don't know at this point. But my research program at CAMH is hoping to move the needle a little bit on this and try and understand a little bit about what the key components of the antidepressant response in psilocybin assisted therapy is.

David Gratzer: And you've got funding for that?

Ishrat Husain: Yes, we were really excited to learn that last year we became the first group to receive federal funding in Canada to conduct a clinical trial of psilocybin, which was really great, and that the trial that we are proposing is aiming to address that question which I just posed, which is whether subjective psychedelic effects are needed to achieve an antidepressant effect with psilocybin.

David Gratzer: And, you know, in a pivot, this is an exciting moment in your career. So, yes, there's funding for that work. And of course, you were a co-author in the *New England Journal of Medicine* paper. What was that like?

Ishrat Husain: It was it was very rewarding to see that all of the hard work we put into that study, which was, honestly, I can't tell you how much work it was to be the first academic institution in Canada to conduct a clinical trial of psilocybin since at least the mid 20th century. It took an army, it took a lot of patience, a lot of hard work to get this study off the ground. Then also, obviously in the middle of a pandemic, which essentially halted all research activity for a while as well. It was a relief that it was rewarded with a publication in the *New England Journal*. But also it was a great experience for us at CAMH. You know, it really did set the framework for us to be able to launch a program of psychedelic science research. It gave us the experience of how to actually deliver this intervention, what resources are required, what infrastructure is required. And it was a great

learning experience for that. And then to collaborate with esteemed colleagues from Europe, North America, really speaks to the nature of how team science can actually be so impactful. So overall, it was a challenging but rewarding experience.

David Gratzer: Samuel Clemens, who of course, writes under the pen name of Mark Twain, once commented that a classic was a book that you want to have read but don't want to read. Was this a really good experience that you want to have had but don't want to go through again?

Ishrat Husain: Yeah, I mean, to be honest, I think the next time around is going to be a lot easier. We learned a lot along the way, and I think that I've assigned myself to a couple more rounds of doing it, so I don't think I can get away from it at this point!

David Gratzer: On a pivot back to clinical issues, we've talked about patients talking about psilocybin, something else that's being more widely reported, and patients are discussing with this is the concept of microdosing, not just this drug, but other drugs, certainly very fashionable in certain cultures within our culture, including those in the tech industry and so on. What are your thoughts?

Ishrat Husain: I'm approached about that when people hear socially that this is an area of research. I'm involved in an approach all the time. People asking me about the benefits of microdosing, about how they microdose and how anecdotally they feel it's really impacted their own wellbeing. But if you look again objectively at published literature, microdosing psychedelics like psilocybin or LSD are not superior to microdosing a placebo essentially in terms of emotional, psychological or cognitive benefits. So I think a large part of it may in fact be the placebo effect that the general or recreational microdosers are experiencing. But if you look at the data, we can't confidently say that microdosing is a healthy habit that that people should do to enhance their mental well-being. There is a study currently underway here in Toronto looking at that, the effects of microdosing and depression, and I know other sites across the world are looking to answer this question, but at this point it doesn't look like it does much above placebo.

David Gratzer: Dr. Husain, it is, as you know, a Quick Takes tradition that we end with a quickfire minute where we ask several questions in a row. We're going to put a minute on the clock. Are you ready?

Ishrat Husain: I'm ready.

David Gratzer: All right, here we go. Do you think we'll be talking about psilocybin in five years' time?

Ishrat Husain: Yes.

David Gratzer: Do you think ultimately scalability will be a major issue?

Ishrat Husain: Yes.

David Gratzer: Oddest request from a patient who's aware you're doing research in the area?

Ishrat Husain: Asking if they should be buying mushrooms from their neighbour who grows them to see if it would benefit their anxiety.

David Gratzer: You do a lot of media: most unusual comment from a member of the public or one of your patients about something you've said?

Ishrat Husain: The most unusual comment has been that why I'm not advocating for psilocybin to be accessible to the general public for recreational use.

David Gratzer: Biggest worry?

Ishrat Husain: That psilocybin goes the route of cannabis, meaning that it's on available on every street corner and that occurs before we know it's safe and effective, that it halts all research and prevents us from answering some very key questions.

David Gratzer: And that's the minute and that's the interview. Really appreciate your time. On a personal note, I think back to our early days at CAMH, you and I had joined roughly at the same time, and we both had small offices and we'd occasionally chat in the hallway. And now, look, you're doing interesting things published in the *New England Journal of Medicine*, and you've got a corner office. However, as you can see, I'm still in a small office.

Ishrat Husain: Not for long though, David I don't think so!

David Gratzer: Really appreciate your time, Dr. Husain, and really appreciate the thoughtful comments on this much hyped topic.

Ishrat Husain: Thank you very much.

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