

Expert Opinion on Psychedelic-Assisted Psychotherapy for People with Psychotic Symptoms

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Abstract

Background

Currently, personal or familial histories of psychotic symptoms are exclusionary criteria for most psychedelic clinical trials, studies, and treatment programs. This study sought to determine why such an exclusion exists, what the implications of the exclusion criteria are, and if there was agreement in expert opinion.

Methods

In-depth interviews with 12 experts in the fields of psychiatry, clinical psychology, medicine, and the effects of psychedelics and entheogens were conducted in an expert consultation format. Interviews were transcribed and themes were produced using an Interpretative Phenomenological Analysis (IPA) approach.

Results

We found that while the exclusion criteria may be justified for psychedelic protocols that provide insufficient psychological support for participants, there was agreement that psychedelic-assisted psychotherapy is not necessarily contraindicated for all individuals with psychotic symptoms. Results suggest that highly supportive psychedelic-assisted psychotherapy may be of benefit to individuals experiencing symptoms of psychosis. Potentially relevant factors for predicting treatment outcomes include specific symptom endorsement, illness duration, symptom severity, quality of the therapeutic alliance, role of trauma in symptom etiology and perpetuation, and the level of other supports in the life of the client.

Introduction

After the occurrence of the First Wave of Psychedelic Research, which began in the 1950s and subjected hundreds if not thousands of persons with severe and persistent mental health conditions to inhumane experimentation with psychedelic substances [1], persons with psychotic symptoms were systematically excluded from psychedelic studies [2]. Reasons for exclusion vary and may include the tendency of clinicians and researchers to be highly cautious as well as misperceptions forged during early psychedelic research along with the political and legal machinations that followed. It was also during this time that the conceptualization of psychedelics as psychotomimetic, i.e., mimicking psychosis, was widely disseminated in scientific literature and later brought into the public sphere by popular media and political campaigns [3]. One misperception that appears to persist is related to overestimating the likelihood of psychedelic compounds catalyzing psychotic symptoms in episode-prone individuals, despite the lack of methodologically sound studies demonstrating this in controlled client-centered

clinical settings [4]. Data below indicate however that psychedelic-induced destabilization occurs almost exclusively in naturalistic settings and is usually characterized by misuse or abuse. Moreover, within Indigenous communities, such as those in the Amazon Basin or in Siberia, psychotic experiences such as hearing voices are not stigmatized or pathologized and instead, individuals with hallucinations are understood as spiritually adept and may not only partake in psychedelic plant rituals but may even lead and facilitate such ceremonies, without any evidence of a worsening of their psychosis [5,6]. While the past century is a pertinent time period to keep in mind in the context of psychedelic clinical research, it is just as important to recall living traditions and their thousands-years old histories and practices.

Exclusion Criteria for Psychedelic Research and Practice

Ethnoracially diverse participants have been underrepresented in psychedelic studies, demonstrating the need for revising practices in order to promote greater inclusivity [7,8]. In addition, only individuals with narrow psychiatric diagnoses qualify for the vast majority of psychedelic studies even though such treatments may be helpful in treating other similar diagnoses and mental health conditions [9]. Currently 3,4-Methylenedioxymethamphetamine (MDMA) is considered a breakthrough treatment for only those with treatment-resistant posttraumatic stress disorder (TR-PTSD) [10], while psilocybin is being explored primarily for treatment-resistant major depressive disorder (TR-MDD) [11,12]. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5, American Psychiatric Association, 2013) encompasses far more conditions than those being included in psychedelic clinical trials as of 2021, many of which share similar symptomatic clusters, etiologies, and phenomenology, warranting an investigation into whether a broader range of patients could benefit from psychedelic-assisted psychotherapy (PAP) [13].

Mitchell and colleagues [14] found that individuals with the dissociative subtype of PTSD responded best to MDMA-assisted psychotherapy, which may also be grounds for hypothesizing that individuals with psychotic-type dissociative symptoms, such as with borderline personality disorder, may respond similarly. However, this line of research has not yet been explored and psychotic symptoms remain largely unstudied in the context of PAP and this lack of scientific attention has important consequences. For instance, African and Latin Americans are three times more likely to be diagnosed with psychotic disorders than White Americans of European descent [15], thus the exclusions of psychotic symptoms in PAP has a direct impact on BIPOC communities' participation in psychedelic research.

Psychotic Symptoms as Exclusion Criteria

With the growing shift from a purely pharmaceutical approach to integrated approaches included psychotherapy, supported by an abundance of empirical studies demonstrating the effectiveness of psychotherapy for psychotic symptoms [16], it is time to reconsider when and how patients with psychotic symptoms and psychotic spectrum disorders (see Appendix 1) may benefit from psychotherapy coupled with psychedelic dosing and integration sessions. For example, Acceptance and Commitment therapy (ACT) has recently been shown to be effective for people with psychosis [17]. Given that ACT's central focus is on developing psychological flexibility and that psychedelic dosing sessions

have been demonstrated to enhance psychological flexibility [18,19], these two approaches in combination may be particularly useful for people experiencing symptoms of psychosis.

Definitions of psychosis and psychotic symptoms are culturally bound. In the Western world, psychotic symptoms are heavily stigmatized and associated with many misperceptions. For instance, individuals with psychosis are typically viewed as dangerous, despite evidence that, on the contrary, these individuals are more likely to be victimized themselves [20]. Indeed, people with psychotic symptoms are more often violent towards themselves rather than others, with deliberate self-harm being observed in approximately 10% of patients, along with high rates of suicidal ideation and alcohol abuse [21].

Experiences that would be labeled as psychotic in Western psychiatry are readily observed in Indigenous communities around the world where they are understood differently. In some cultural contexts, especially in peoples practicing shamanism, many individuals with psychotic experiences like hallucinations are not seen as mentally ill, but are rather viewed as possessing unique spiritual abilities that permit them access to different channels the average person cannot [22,23]. It is also interesting to note that the majority of delusions (60%) associated with psychotic symptoms fall within the theme of religion and spirituality [24]. While such beliefs are stigmatized and deemed as being out of touch with reality in the West, other more religious societies may view such beliefs differently. For example, in Tibet the Dalai Lama is not viewed as being psychotic due to the fact that he sees himself as the reincarnation of the Buddha of Compassion. However, an individual in America claiming to be the son of God would almost certainly be deemed delusional. Although hallucinations during grief are viewed as relatively common and normal within mainstream Western psychiatry, in some societies, auditory hallucinations of deceased family members or friends are not viewed as being the result of a mental illness, but are considered insightful and are taken seriously [25,26].

Etiology of Psychotic Symptoms

Psychosis has many definitions as it exists on a spectrum, ranging from brief experiences of atypical perceptions to chronic and pervasive psychosis. In modern clinical practice, reflected in both the World Health Organization (WHO) and the American Psychiatric Association (APA), the most common definition of psychosis refers to delusions and/or hallucinations with impaired insight [27], which vary markedly in presentations, severity, and evolution. For instance, more than 1 in 10 people report experiencing auditory hallucinations at some point during their life [28], whereas primary psychotic disorders, often featuring severe and chronic symptoms of psychosis, have a lifetime prevalence of approximately 3% [29].

Psychotic disorders are polygenic, caused by complex interactions between multiple biological and psychological factors [30]. These causes converge in a wide variety of higher-level effects on neural oscillations and circuitry, which are in turn reflected in changes in cellular machinery down to the level of ion channels, and transcription changes [31]. Over 100 genetic sites have been identified as contributory [33,34,35,36]. Beyond genetics, substances, pathogens, and/or psychological trauma also result in alterations to synaptic connectivity. Developmental processes can likewise result in abnormal synaptic

connectivity, e.g., excessive synaptic pruning has been implicated in the development of schizophrenia [36].

The entropic brain theory suggested by Carhart-Harris and colleagues (2014) posits that brain activity, cognition, and behavior exist on a continuum, with one end characterizing people who are notably rigid and the other, those who are in a state of high entropy or chaos. Individuals with psychotic symptoms are thought to fall into the latter category according to this model, which is grounds for some clinicians to see psychedelics as likely to potentiate and exacerbate psychosis for those with symptoms or a disposition regardless of set and setting. Contrary to the entropic brain theory hypothesis, psychotic symptoms could be interpreted as a highly fixed state of mind, as people with psychotic symptoms may also be seen as endorsing rigid sets of behaviors and beliefs given that DSM-5 defines delusions as “fixed beliefs that are not amenable to change in light of conflicting evidence [37]. As such, there may be fundamentally sound reasons to include, rather than exclude persons with psychotic symptoms such as psychedelics’ ability to increase psychological flexibility [18].

Alternative hypotheses that define psychosis as brain diseases due to correlations with the loss of grey matter posit that purely pharmaceutical treatment approaches are most effective, despite neural and genetic findings being largely nonspecific, inconsistent, and of small magnitudes [38,39]. The notion that forms of psychosis such as schizophrenia are progressive brain diseases has also been challenged [40]. Indeed, the emphasis on putative neurological abnormalities as causes of psychosis, as well as the interest in brain-based explanations of psychedelic effects such as the entropic brain theory, may be reflective of psychiatry’s turn to the brain, which prioritizes biogenetic etiological understandings of psychological experiences [41]. In contrast, increasing evidence demonstrating that psychosis is a product of both environmental and biological genetic causes have generated renewed interest in the role of environmental influences on psychosis, particularly trauma [42]. Integrative models that view trauma as interacting with biological vulnerabilities as causal factors in psychosis have clear implications for psychedelic clinical research, suggesting that chemical compounds found to be helpful in resolving trauma such as MDMA may be effective tools against psychotic symptoms when used in combination with appropriate psychotherapeutic support.

Trauma as a Causal Factor in Psychosis

A wealth of literature supports a robust correlational relationship between childhood trauma, particularly sexual abuse, and psychosis [43,44,45,46]. Individuals who have experienced at least one traumatic event are more likely to exhibit psychotic symptoms and have a 20% increased risk of persistent mental/emotional stressors relative to the general population [47,48,49]. Likewise, people with psychosis are approximately three times more likely to have experienced childhood adversity than controls. Despite the growing evidence for environmentally facilitated psychotic symptoms, one reason why a narrow biogenetic-origins model may be more commonly accepted within psychiatry is that current psychodiagnostic nosology blurs the line between the model of trauma-induced psychosis and PTSD [50]. For example, it is possible that the DSM-5 criterion of the presence of “marked stressors” for brief

psychotic disorder mischaracterizes the potential for delayed onset (prolonged gestation) of the effects of trauma in people presenting with psychotic symptoms. Cases of trauma being the primary precipitant for the development of hallucinations, dissociation, delusional thinking, and similarly debilitating symptoms generally lead to a diagnosis of PTSD, raising questions about the meaningfulness and utility of drawing clear distinctions between psychotic disorders and PTSD. Furthermore, the highly filtered recognition of traumatic events that, as an example, excludes experiences of racism and discrimination, undermines the far-reaching complexity and variety of trauma [51,52,53].

Cognitive behavioral therapy (CBT)

Psychosocial interventions including psychotherapy are now considered essential in the treatment of primary psychotic disorders, in combination with medications [54]. Cognitive behavioral therapy (CBT) with its focus on symptom management has demonstrated improvements in tackling delusions and hallucinations while mitigating the side effects of traditional antipsychotic drug treatment [55]. In psychosis, CBT is often used in conjunction with pharmacological interventions as pharmacological and psychosocial interventions are seen as synergistic and interactional. Such combined approaches are motivated by the fact that many people with psychotic disorders seek reassessment of care models focused primarily on pharmacological treatment due to unsatisfactory results and side-effects [56,57]. The last revolutionary moment in psychosis treatment was the discovery of the atypical neuroleptics in 1951 [58]. While neuroleptics were seen as breakthrough therapies at the time and led to deinstitutionalization, evidence accumulated in the intervening years has resulted in a re-evaluation of treatment models focused solely or primarily on antipsychotic medications.

Ketamine

Ketamine has demonstrated multiple avenues of treatment for patients with bipolar disorder (BD) and schizophrenia [59,60,61,62]. The symptoms of depression and suicidal ideation in treatment-resistant BD patients have been shown to be reduced within a single day of an subanesthetic intravenous ketamine infusion [63]. Ketamine's drastic benefits are attributed to a wide array of interconnecting systems, targeting glutamate pathways, promoting neuroplasticity and synaptogenesis, epigenetics, immunomodulation, and kynurenine pathways [63,64]. Unipolar and bipolar depression, which can often feature psychotic symptoms, can be effectively treated with ketamine due to its ability to target resistant depression while regulating anxiety, inflammation, and agitation [60].

Ketamine antagonizes the glutamate receptor NMDA by increasing the synaptic release of glutamate [65], while suppressing its effects at glutamatergic excitatory synapses. In the context of clinical trials, ketamine is explicitly designated as a treatment for suicidal ideation, as it has been shown to decrease suicidal ideation by 79% while improving cognitive deficits of depression, potentially by increasing neuroplasticity [66,67]. The compound may present a unique profile for its use in people with symptoms of psychosis, for example by providing a period of respite, whereby one abides in a state of altered awareness that may in turn promote one's ability to engage in the therapeutic process and develop novel perspectives during psychotherapy [68]. Ketamine is known to be generally safe and effective with a wide

variety of psychiatric medications, including some serotonin reuptake inhibitors (SSRIs), antidepressants, anxiolytics, antipsychotics [69,70,71].

Studies show that subanesthetic doses of ketamine in both schizophrenic and non-schizophrenic patients induces a temporary, dose-related altered state commonly referred to as dissociation [59,61]. Although there is some debate, many studies suggest that the actual experiences of ketamine-induced “dissociation”, which may be better conceptualized as bodily transcendence, underlie its benefits [72]. Though no research supports ketamine possessing therapeutic benefits for psychosis directly, successful treatment of unipolar and bipolar depression with psychotic features with ketamine has led to resolution of psychotic symptoms likely by treating the underlying mood symptoms [73,74]. Ketamine-induced “dissociation” or experiences of material transcendence in schizophrenic patients is transient, does not appear to result in distress, and resolves within a few hours post-infusion [75,76,77]. Ye et al. [62] also found ketamine to have positive, though temporary, effects on individuals with chronic treatment-resistant schizophrenia.

MDMA

There is some reason to believe that psychedelics may be effective in treating PTSD comorbid with certain symptoms of psychosis. In particular, 3,4-Methylenedioxymethamphetamine (MDMA)-assisted supportive psychotherapy as observed in breakthrough treatments for refractory posttraumatic stress disorder (PTSD) may be useful in treating psychotic symptoms with co-occurring trauma due to the two groups sharing highly similar symptomatic clusters, etiologies, and phenomenology [12]. MDMA’s ability to create an emotionally safe space to foster unmitigated vulnerability with therapists, allows for traumatic memories to be processed, putatively by releasing oxytocin [78], and decreasing the activity of the amygdala thereby reducing the overall response to stress, fear, and anxiety [79,80,81]. In this sense, MDMA-assisted supportive psychotherapy, which utilizes strategies and techniques from modalities that have proven efficacy in psychotic disorder such as CBT, may be useful in treating trauma with co-occurring psychotic symptoms.

Purpose of the Study

The purpose of this study is to explore opinions about excluding people with a personal or familial history of psychotic symptoms from participating in psychedelic clinical research and experimental treatments. We asked when psychotic symptoms are justified as an exclusion criterion for psychedelic clinical studies and treatment programs and why and when such a position may be warranted.

Method

Study Design

The study design utilized an expert consultation approach, which involved interviewing participants considered to be experts in the field. Due to the high degree of specificity of knowledge, expertise, and

training required to answer the questions involved in the study adequately, sampling was not random and only known experts with significant experience or interest in working with psychedelic compounds or psychotherapy were contacted to participate. Participants were asked specifically about the validity of current exclusion criteria, whether they believed psychedelic-assisted psychotherapy could be effective for individuals with psychotic symptoms, and, if so, how such a study or protocol could be carried out safely and effectively. A total of 12 participants were recruited. Questions were based on a semi-structured interview format template (See Box 1).

Ethical Consideration

Written informed consent forms were collected prior to the interviews, as well as verbally verified at the start of the interviews. Interviews were audio-recorded and subsequently transcribed. Participants were free to withdraw from the interview and request to not be recorded. This study was approved by the Research Ethics Board of the University of Ottawa.

Box 1: Applicable Interview Questions About Psychedelics and Psychotic Symptoms

PAST CLINICAL EXPERIENCE

- Have you ever helped someone with psychotic symptoms through a psychedelic experience?
 - What contributed to it being positive or negative?
- Have you had any clients with a traumatic component to their psychotic symptoms?
 - How do you find that it affects how they experience psychedelic psychotherapy?
 - How did you find that psychedelic therapy affects their trauma/psychotic symptoms?
- Have you ever had a client with psychedelic-induced psychotic symptoms?
 - When might psychedelic-induced psychotic symptoms occur? (E.g., does it usually occur outside of clinically controlled settings?)
- How might hallucinations from psychotic symptoms affect psychedelic hallucinations or vice-versa?

THEORETICAL

- Are psychedelics compatible with psychotic symptoms? If so, why? If not, why not?
- If you were to develop a psychedelic intervention for psychotic symptoms, what would that look like?
- What would an ideal sample look like for an initial trial? (i.e., stable for how long, how mild, how old, etc.?)
 - Who do you think would be a safe candidate with psychotic symptoms, and why? (severity, duration, symptomatic/diagnostic profile, etc.?)
- Do you think MAPS and other protocols that use psychotic symptoms as an exclusion criterion across the board are fair/justified? Why or why not?
- What are some risk factors that might be a red flag in people with psychotic symptoms?
 - What about in general?
- How do we work with someone with psychotic symptoms who is on medication?
- What pre-existing medical conditions might contribute to there being the possibility of a challenging experience occurring?
- How might age influence candidacy?
 - Any negative effects on psychedelics on the brain at a later age?

Qualitative Analysis/Procedures

Recordings of interviews were automatically transcribed using transcription software and subsequently reviewed by two members of the research team for accuracy. Experts' experiences, opinions, and other

results were coded using an Interpretative Phenomenological Analysis (IPA) approach [82]. Major themes were identified throughout the transcripts and subsequently coded. Statements that fell under the same theme were synthesized into a narrative that reflected the variety of participants' opinions and were subsequently included in the results section of the paper. Some statements were included in multiple themes if they were relevant to more than one.

Results

Details About the Expert Participants

For this study we included 12 participants living in the United States and Canada. Participants were affiliated with several respected institutions, including Johns Hopkins University, California Institute of Integral Studies, Yale University, and University of Toronto. Ten are also affiliated with clinics, hospitals, or are in private practice. Participant selection was deliberate and was based on having expertise in clinical psychology, psychedelic compounds, psychotic symptoms, and/or medicine. Out of the 12, three participants possessed credentials and experience that demonstrated expertise in all four areas, namely a medical degree combined with substantial clinical experience with individuals with psychotic symptoms and psychedelic compounds. One participant possessed area expertise in all three except psychotic symptoms, three possessed expertise in two areas, and three possessed expertise in one. Two participants had lived experience with psychotic symptoms. The mean number of years participants had worked as a healthcare professional was 23 years, out of which 92% had direct experience with the therapeutic effects of psychedelics. Table 1, below, demonstrates the demographic and relevant experience characteristic of the study experts.

Table 1 *List of Experts Interviewed*

ID	Gender	Race / Ethnicity	Position	Years of Experience as a Healthcare Professional	Years of Direct Experience with Psychedelics
1	Male	White	Psychiatrist	7	5
2	Male	White	Clinical Psychologist	17	12
3	Male	White	Psychotherapist	21	7
4	Male	White	Psychiatrist	62	63
5	Male	White	Psychiatrist	53	53
6	Male	Asian	Psychiatrist	5	2
7	Female	White	Psychotherapist	16	5
8	Male	White	General Physician	9	0
9	Female	White	Minister, Spiritual counselor	0	25
10	Male	White	Doctor of Nursing	24	7
11	Male	Hispanic	Physician	18	28
12	Female	White	Doctor of Nursing	44	55
Total Years:				276	263

Note. This table demonstrates the number of years spent by 12 participants from varying fields of expertise as Healthcare professionals and Psychedelics investigators.

Themes

Interviews uncovered a broad consensus surrounding six discrete themes as highlighted in Table 2. These included (1) the need for structured guidance that must be established during psychedelic treatments (2) the potential influence of physical and emotional trauma on the development of psychotic symptoms (3) the history of psychiatry and the problematic terminology, pathologization, and stigmatization of psychotic experiences (4) inclusion and exclusion criteria for psychedelic treatment (5) the entropic brain theory as it relates to the effect of psychedelics on people with psychotic symptoms and (6) the differences and similarities between psychotic episodes and experiences of spiritual emergence.

Table 2 *Verbal interviewee responses to the questions regarding psychedelic-assisted psychotherapy for psychotic symptoms*

Theme and description	Exemplar quotes	Number of respondents
<p>Safety/Guidance</p> <p>Psychedelic treatment and assessment guidelines for patients with psychotic symptoms</p>	<p><i>"I think a huge thing would be family and peer support and community support. If they don't have a strong support network it's more of a concern"</i></p> <p><i>"You must have a great deal of safeguards in place for the person, including an early trigger for hospitalization and then perhaps the ideal place to treat psychosis, it would be on an inpatient basis"</i></p>	<p>5 (42%)</p>
<p>Trauma</p> <p>Association of experienced trauma and psychotic symptoms</p>	<p><i>"It [psychedelic-assisted psychotherapy] can be helpful for people who have a history of trauma"</i></p> <p><i>"We bring traumatic memories up from the poorly stored locations in the left amygdala. We bring them into an MDMA environment where there are two therapists, who are supporting the person"</i></p>	<p>4 (33%)</p>
<p>History of Psychiatry</p> <p>Systematic reassessment of psychotic diagnoses and treatment protocols</p>	<p><i>"These are terms [psychosis] that are over a century old"</i></p> <p><i>"There should be an ability to build up rapport. Old psychoanalysis would say it is just kind of defined psychosis, as this is somebody that you can't psychoanalyze. They lumped together all of these different conditions"</i></p>	<p>4 (33%)</p>
<p>Psychotic Symptoms as an Exclusion Criterion</p> <p>Need to revise, rethink and nuance protocols, nosology, and phenomenology of psychosis</p>	<p><i>"For these one-shot situations, I think the exclusion criteria are appropriate"</i></p> <p><i>"What would be the effects of psychedelics on people who hear voices, who actually don't meet criteria for psychedelics for psychotic disorders? Versus someone who predominantly has delusions versus someone who's more paranoid?"</i></p>	<p>2 (17%)</p>

Entropic Brain Theory Reassessment of the entropy based descriptions surrounding psychotic states	<i>"I have colleagues in the medical field who have been diagnosed with bipolar disorder. They both use psychedelics to positive effect"</i> <i>"The person who does have a dysfunctional default mode network in the chaotic range, give them a powerful psychedelic substance...break down their default mode network and when it's being reconstructed, direct this person's experience into a more positive mode"</i>	2 (17%)
Psychedelics and Spiritual Emergencies Differentiation between psychotic symptoms and spiritual emergence, Delusions determined by cultural context	<i>"What makes the difference in our view between spiritual emergence and psychosis is that in spiritual emergence, there remains at some level a sense of center, a sense of self"</i> <i>"People will meet the textbook criteria for psychosis, but they just happen to have a spiritual emergency and actually the MDMA or psilocybin would be the best solution"</i>	3 (25%)

*Note: n=12, LSD: Lysergic acid diethylamide, MDMA: 3,4-Methylenedioxymethamphetamine

Psychotic Symptoms as an Exclusion Criterion

Findings indicated that the exclusion criterion barring the participation of people with psychotic symptoms from current psychedelic clinical studies designed for PTSD, anxiety, and depression might be justified since they typically do not provide enough support for this especially vulnerable and high-risk population. Participant 5 noted, "It's not because we fear that psychosis is necessarily contraindicated..." Several other participants echoed this sentiment saying that in a context where there is substantial support in place, psychedelic-assisted interventions could be both safe and effective for people with symptoms of psychosis. Participant 4 noted that psychotic symptoms are an exclusion criterion in various clinical trials, studies, and treatment programs, which offer psychedelic dosing sessions on an outpatient, short-term basis because the protocols do not offer enough support. For example, a context where such treatment is provided on an inpatient basis and the clinician uses the compound as an adjunctive to long-term supportive psychological work with a person could produce different results from when taken as part of a less supportive program some participants noted. Participant 4 elaborated by saying that the exclusion criteria for less supportive contexts, which provide a "one-shot" or "weekend" experience are justified because "you really don't know what you are going to be dealing with and you don't know how you are going to close or whatever you are going to open." Participant 7 also mentioned an inpatient context as being effective and that the protocol could be akin to treating substance use disorders.

Participant 1 said that it is probably not true that people with psychotic symptoms cannot receive psychedelics safely and pointed out that part of the reason for the situation at hand may be due to FDA's

criteria requests. On this matter, participant 7 said, “Psychiatrists tend to be quite conservative...” and said, “Why should we deny people the opportunity to have those numinous experiences? That’s gatekeeping. That seems like really egregious gatekeeping. I think it would, again, be on an individual basis. And why shouldn’t we all have the opportunity to have those mystical experiences?”

When asked about the possibility of data demonstrating safety and efficacy of MDMA for PTSD being relevant to psychedelic-assisted psychotherapy for psychotic symptoms, participant 12 replied, “Why is the field of psychedelic medicine currently lionizing MDMA for PTSD and not for psychosis, another diagnostic category in which many of the defining symptoms are the same and it’s forbidden? How did we get there?”

Definitions of Psychosis

One central theme that was raised throughout the interviews was the definition of psychosis. Participants often brought up the heterogeneous nature of psychosis as a category of experience and how the term can mean something different depending on who you ask. Participant 3 discussed how psychosis is on a continuum and that different people draw the line of what is defined as psychosis at different places. Participants 4, 5 and 9 all mentioned that a spiritual emergence must be differentiated from psychosis while participant 3 did not find this distinction useful or helpful.

Participant 6 said that, “There are clusters of psychosis that don’t look like each other” while participant 1 talked about how “DSM diagnoses are not single disease entities, so not everyone with a diagnosis of schizophrenia is the same.” For example, several participants mentioned that some individuals may have paranoid delusions and others hallucinations. Participant 4 said, “psychosis doesn’t really tell me anything useful as to what’s going to be helpful to the person” and that, “These are terms that are over a century old – before the car, before the light bulb.” Participant 6 also noted the diversity of psychotic experiences, saying that “One person reporting voices may not be at all the same thing. Like somebody that’s saying, ‘I hear voices that remind me of the thing that happened’ versus somebody that’s mumbling to themselves who keeps looking over to the left of the room. You’re talking to them, they keep getting distracted, it literally looks like they’re hearing something and they’re kind of talking back and they’re trying not to show you they’re doing that. Those are so different. And so lumping them together as like, ‘hearing voices’ is [not the same].”

Several participants mentioned the importance of whether symptoms are interfering with the patients’ life or are distressing, noting that not everyone who has psychotic symptoms would meet criteria for a DSM-5 psychotic spectrum disorder diagnosis. For example, participant 1 pointed out that, “we know that hearing voices, for instance, is a spectrum.” Other participants discussed how psychotic symptoms may not necessarily be debilitating and how they can actually be beneficial by providing insight and creativity. For example, participant 4 mentioned when referring to relatives of patients with psychosis they interviewed, “in a way, had more hallucinatory experiences than the patient, but they were not interfering with their life. They actually benefited from that because it generated some creative ideas that they could apply in their business, in their writing.”

Participant 12 spoke about how psychosis can be framed as “just receiving channels that other people don't acknowledge.” and that, “It doesn't necessarily mean that they [the channels] don't exist.” They continued to speak about how reality “tends to be socially determined” and how a lot of this [psychosis] is “definitional.” They talked about the example of someone who could see auras of people and what that would be—an experience of psychosis or an extrasensory ability— and mentioned how this person’s “perceptual apparatus would be truncated” if this ability did not exist and how within a psychiatric framework, this would likely be reduced to a hallucination.

Psychedelic-assisted Psychotherapy for Psychotic Symptoms

Participants' responses reflect that psychedelic-assisted psychotherapy may be beneficial for some individuals with psychotic symptoms under the right conditions. Participant 2, a licensed psychedelically-informed clinical psychologist and experience with leading psychedelic clinical trials, said that:

If we're talking about moderate or mild psychotic symptoms, then I certainly think that you could control the setting and provide the type of ongoing support and care for an individual and I think that could be a really interesting line of study. Eventually, down the road, we're going to need to test whether this is actually true, whether the fear that people have about even severe psychosis or severe risk for psychosis is something that psychedelics bring about when you're giving psychedelics as part of a therapeutic program. I think that to my knowledge, a lot of the concern comes from evidence in recreational and non-controlled settings where there have been some reports of problems but I don't know that's going to be the same when we have it in controlled clinical environments.

Participant 3 mentioned they could see psychedelics being useful in helping to loosen up delusional states saying that “they also might be able to [see] some delusion they've been stuck in....they might open up to a whole bunch of different perspectives and realize there's actually all these different ways of looking at it.” Participant 4 said, “if you had somebody with some hallucinatory experiences, but he is functioning well at work and functioning well in the family, it [the psychotic symptom(s)] is irrelevant and of course you could use psychedelics.” In addition, they mentioned that “there is such a spectrum and people will meet the textbook criteria for psychotic symptoms, but they just happen to have a spiritual emergence and actually the MDMA or psilocybin would be the best solution for that.”

At the same time, while psychedelics may not be contraindicated for psychotic symptoms as participant 5 mentioned, they also said “you must have a great deal of safeguards in place for the person.” Participant 3 likened the psychedelic experience to meditation noting that “when people get into deeper water without guidance, that's when that sometimes, they really, you know [get destabilized]...so it makes me curious that, if, maybe the same thing would work with psychedelics and that you would just need more attention... And only when people are in that fragile state because some of those same people that have had a psychotic episode...but now they are much more grounded... You hear about them going on long meditation retreats and being fine.”

According to the participants' responses, simply identifying whether there is a history of psychotic symptoms or endorsement of psychotic symptom(s) is not as relevant for determining if the individual will be a good candidate for psychedelic-assisted psychotherapy as whether symptoms are distressing, debilitating, or causing life impairment. Instead, clinicians should remember the heterogeneous nature of psychotic experiences and assess specific symptom endorsement together with levels of functioning. As participant 6 said, "Psychotic depression I could imagine psilocybin being useful for in a way that psychotic mania, I just can't," demonstrating how some within this group could be at higher risk than others depending on their specific experience and the need to assess candidacy on a case-by-case basis. It also demonstrates how different compounds could be useful in different situations. In addition, whether symptoms are debilitating must also be taken into account.

While participants mention that psychedelics could certainly be used by individuals with psychotic experiences that are not debilitating, it is also important to note that people on the more severe end of the spectrum may not necessarily be contradicted either. As participant 6 mentioned, "for chronic psychosis, I mean, we have nothing to go on from modern studies about that." Participant 2 also said that eventually we are going to need to test whether psychedelic-assisted therapy could help people with mild, moderate, and severe psychosis. This is because there is not enough data to dismiss the possibility of psychedelic treatment being beneficial to those with chronic psychosis, only fraught data collected during the First Wave of Psychedelic Research [1].

When asked about the possibility of MDMA being effective for psychotic symptoms in a way similar to PTSD, participant 12 said: "[this] project is the first time that I've ever been brought to consider that, and I can't imagine why no one has, but I've certainly never thought it would before but it seems utterly obvious that that should be the case." Participant 10 suggested psychedelics facilitating a kind of purge where the psychotic symptoms are released all at once, and participant 12 mentioned something similar where an individual might "move through" the experience and have an outcome that enriches the person.

Potential Effects of Various Psychedelic Compounds on Psychotic Symptoms

Participants were asked about what specific psychedelic compounds might be beneficial to individuals with psychotic symptoms and several suggested MDMA. Table 3, below, demonstrates the themes identified in the study using a thematic analysis approach.

Table 3 *Verbal Interviewee Responses to the question arguing for the effectiveness of various psychedelic adjunctives in treating psychotic symptoms*

Theme and description	Exemplar quotes	Number of respondents (percentage of total sample, n=12)
<p>MDMA*</p> <p>Facilitates the processing of traumatic material</p>	<p><i>"MDMA are more likely to have positive emotions, so it's not as likely to activate negative memories"</i></p> <p><i>"MDMA produces this sense of safety that allows people to explore things that otherwise are kind of frightening"</i></p>	<p>5 (42%)</p>
<p>Ketamine</p> <p>Use for psychotic symptoms</p>	<p><i>"Ketamine is something that does seem less likely to push people into scrambled states"</i></p> <p><i>"I recognize for one thing, that Ketamine is an abusable drug and it's difficult to abuse serotonergic psychedelics because the brain just won't let you do it"</i></p>	<p>1 (8%)</p>
<p>Psilocybin</p> <p>Positive outcomes despite being a challenging experience</p>	<p><i>"It was complete torture to this person, and yet they had a complete remission of their depression"</i></p> <p><i>"Memories are restored, they are altered by the experience of the psychedelic work and are not stored in the same way that they were when they were first done"</i></p>	<p>4 (33%)</p>
<p>Ayahuasca</p> <p>Risk of destabilization but may still be therapeutic</p>	<p><i>"Ayahuasca is on the heavy-duty side of triggering such episodes [psychosis], versus MDMA that is maybe a little more mellow. Ayahuasca, is a high risk"</i></p> <p><i>"We had this guy who was hospitalized post-ayahuasca and he still thinks it was the best thing that ever happened to him"</i></p>	<p>2 (17%)</p>
<p>Serotonergic Combinations</p> <p>LSD/Psilocybin/MDMA</p>	<p><i>"Psilocybin, LSD, or the classic psychedelics allow the person back to higher entropic state"</i></p> <p><i>"MDMA is an introductory molecule to modify the psychotic state, then I would use psilocybin or possibly combination of the two"</i></p>	<p>4 (33%)</p>

*LSD: Lysergic acid diethylamide, MDMA: 3,4-Methylenedioxymethamphetamine

Participant 5 said that, “If I were to answer your question therefore about which would be the most acceptable, most useful psychedelic, I would say we don't know, but, if you want to produce the possibility of some change, I would think that a drug like MDMA would be the starter molecule.” They also said that “And then if you're looking at trying to modify their psychotic state then I would use psilocybin, or very possibly...a combination of the two (MDMA and psilocybin).” Participant 7 said that MDMA could be useful for its ability to bring about self-compassion, which can be useful for addressing the shame that often comes up with trauma in addition to the stigma of psychotic symptoms.

To further support the possibility of MDMA being effective, participant 2 said, “My bias is that MDMA is a softer first approach to helping people” and that MDMA-assisted psychotherapy is “potentially the only treatment that they need.” Aside from the specific compound, participant 4 stressed that the supportive psychotherapy would also be crucial noting, “I think the best thing, whether it's MDMA or psilocybin, is to offer it as psilocybin- or MDMA- supported psychotherapy where the person would get to know the client well” They mentioned the therapeutic context is important because, the patient “would tell you about their background, their individual development. They would probably tell you about significant things from their family. And then you can decide if it will be helpful to deepen the process by using the MDMA.”

Participant 6 mentioned that MDMA “is almost a perfect drug for trauma in a way that I don't think psilocybin is” and that “MDMA produces this sense of safety that allows people to explore things that otherwise are kind of frightening...” However, when asked about the compatibility of psychedelics and psychotic symptoms, went on to say that “it depends on what we're talking about, but somebody who is acutely psychotic...like they're hallucinating, they have delusions, they're thought disordered....I don't think I could in good conscience give them MDMA.” When asked if entheogens like psilocybin are less relevant than empathogens, they responded, “Not less relevant. I think just, I would imagine it's easier to go wrong. Maybe it's like a high risk, high reward situation.” Participant 4 echoed this sentiment stating that psilocybin could reactivate traumatic memories, though participants 5 and 6 also mentioned scenarios where psilocybin might be effective. Participant 11 noted that Ayahuasca may be the most likely to cause problems for a person with a history of psychotic symptoms and that in contrast, ketamine may be significantly more safe as a compound that seems “less likely to push people into scrambled states.”

When asked about the clinical profiles of specific compounds, participant 12 mentioned that ketamine is an abusable drug. They did not necessarily say this was a good or bad thing or specific to psychotic symptoms, but simply that there is capacity to abuse, which nuances the clinical profile of the drug, namely safety. They also mentioned that “MDMA is in a kind of middle category between [serotonergics and ketamine]” and that it too has the potential to be abused.

Trauma and Psychotic Symptoms

Considering participant 6's comment that "MDMA is almost a perfect drug for trauma," the potential role of trauma in psychotic symptom etiology and symptom maintenance may be extremely relevant to understanding why psychedelic interventions may be effective for individuals with psychotic symptoms. Participant 3 who specializes in psychotic symptom, and has lived experience with psychosis also noted that:

A lot of psychosis is people have a concern, but they're ambivalent about facing it. And so they end up kind of disguising the concern in their mind and turning it into something else, which of course makes them look like they're completely out of touch with reality. And so if they do that successfully enough, then you don't see any connection with the trauma and they don't see any connection with the trauma. And so everybody can say, 'oh, this is just psychosis.' But often as you start working on understanding and healing, you start saying, 'oh, maybe this is connected with the trauma...

They also said that, "Often when they do the research, they say lots of people have PTSD and psychosis, and they talk about it that way, but then they also talk about trauma seems to make psychosis more likely. In fact, having multiple kinds of trauma...the link between multiple kinds of trauma and psychosis is as strong as some of the studies that have found between lung cancer and tobacco" and that, "I think the fact that somebody has lung cancer doesn't mean they smoke. And the fact that somebody has psychosis doesn't mean you're going to find this big prominent history."

Antipsychotics and Biochemistry

Another recurring theme was that individuals with psychotic symptoms are often highly medicated. Participant 6 said that, "you have this silly thing that happens where people have their report paranoia or they report voices. And then that clicks some flips in somebody's head that's like, 'oh, they need antipsychotics.'" Participant 7 made a similar observation saying that, "I think one of the saddest things having worked in the public system for 15 years in outpatient psychiatry is that we often snow them with these antipsychotics. And it might dull them down because they're highly sedating but it doesn't give them any kind of tools to deal with the things that are still coming up." Quoting Aaron Beck, participant 3 described CBT for psychotic symptoms as an alternative treatment being able to "suck the juice out of the delusion," which psychedelic-assisted psychotherapy may be able to help with.

Participant 10 explained that the chemical compounds' effects may differ depending on drug class and how they interact with the brain. Participant 6 discusses amphetamine-induced psychotic symptoms as a concern, noting that if anyone takes enough amphetamines, it could spark something that at least resembles psychotic symptoms. He noted that this would be important to consider since MDMA is an amphetamine. Participant 5, however, noted it would be unlikely for MDMA in the context of psychedelic-assisted psychotherapy to result in amphetamine-induced psychotic symptoms.

Participant 11 also described an instance of ayahuasca-induced psychotic symptoms occurring in South America and the local psychiatrist saying "It is ayahuasca-induced psychosis" and that "if we shut it off, [through the use of sedatives], they will bounce back," and that "it's not really as bad as it looks, we just

need to reestablish the sleep cycle,” though this person was not a good candidate and should have been identified as such. Participant 10 gave similar recommendations stating how important it is to get sufficient sleep the night after the dosing session, as well as an instance where they needed to prescribe an antipsychotic for a week after ketamine and “she was fine.” They also mentioned that for a psychedelic-assisted psychotherapy program for individuals with psychotic symptoms, one should monitor symptoms over time and be prepared to prescribe antipsychotics. Participant 10 also spoke about how it is possible to administer antipsychotics such as Seroquel to stop the psychedelic effects by hitting a similar range of transmitters, but that this will likely have the negative consequence of hampering memory consolidation and so should ultimately be avoided if possible.

Clinical Recommendations for an Initial Pilot Study

Participants gave a multitude of clinical recommendations for an initial study. For example, participant 1 mentioned that some people who hear voices or just have delusions and technically do not meet criteria for a psychotic disorder diagnosis may be good candidates for an initial trial. At the same time, they stressed the importance of targeting specific symptoms emphasizing the difference in symptom clusters such as between treating someone who primarily hears voices versus someone who has delusions and is paranoid. They also noted that the person should not be in the midst of an episode.

Several participants noted that a strong support system would be particularly important. Participant 6 mentioned that in the psychedelic-guide context, “there should be an ability to build up rapport as so much of it seems to be relational...” and described an instance where poor rapport between the therapists and the client resulted in a difficult situation for the client. This may be especially important in instances where relational or interpersonal trauma may be involved in the client’s clinical picture. Participant 12 spoke about how important a safe and controlled clinical setting would be noting that, “The risk is greater when there's nobody on the ground. Somebody should be ‘ground control’, which sort of implies that there would be a prior agreement” and that someone “takes custody of their body while their consciousness goes elsewhere.” They mentioned that another important element is the preparatory part, which would ideally involve “encouraging the person very strongly to allow [confrontation of fears or traumas].” This would likely be key for someone whose psychotic symptoms are primarily a dissociative reaction to a trauma that is too painful to be accepted as true.

Three participants also recommended inpatient support. Participant 12 said “ You have to be prepared that once someone moves into the realm which we identify as psychosis. You have to be prepared to protect and nourish them in a variety of ways for a couple of months.” They pointed out that ultimately though, there is no data on one specific approach to how this would be carried out, (e.g., inpatient setting, daycare-like setting, etc.), and that ultimately this must be taken seriously so as to mitigate any negative outcomes such as harm to oneself or others, which could have tremendous adverse effects for the field of psychedelic medicine. Participant 10 mentioned that in addition to long-term therapy, the possibility of small groups being helpful. As participant 11 mentioned, it would be important to ask questions like, “What is the support network [for this person]? Where is this? Where is this person going to go

afterwards?” and, “Where is this person going directly [afterwards] and who is going to take responsibility for them if they become psychotic?” Further considerations suggested by participant 8, a general physician, include history of drug use, cardiac history, age (over the age of 24 and 30-65 as ideal), family history of sudden cardiac death, assessing for any conditions with an electrolyte panel, signs of infection, current drug usage, presence of tumors, history of homicidal/suicidal ideation, self-harm, presence of weapons at home, social and family support, pharmacodynamics and kinetics of the drugs the potential participant is using, and the metabolism/excretion of the compound in treatment, noting that if the active component of the drug is a metabolite, and the presence of any kidney or liver disease, which may result in the client not being able to excrete the drug as quickly, which may lead to buildup.

Discussion

Cognitive behavioral therapy has been demonstrated to be an effective treatment for psychosis, however it has been underutilized due to political and economic reasons rather than scientific considerations [83]. It is now clear that trauma affects the organism down to the cellular level and multiple studies show that epigenetic changes are correlated with behavioral consequences of trauma exposure [84]. Therefore it is important to emphasize that conceptualizing some types of psychotic symptoms as potentially in part or in large caused by trauma suggests psychedelic-assisted psychotherapy may be a powerful therapeutic alternative, which can, at times, also be used in conjunction with pharmaceuticals.

The etiology of psychotic symptoms matters when considering treatment for the causes rather than the symptoms of the psychotic symptoms. Pure biogenetic-origins models for psychotic symptoms tend to ignore the fact that behavioral therapies also engender lasting biological modifications at the cellular level, and rather look solely to antipsychotics as treatment to provide these changes [85]. A psychosocial, trauma-informed framework, however, is capable of effective cognitive intervention for psychotic disorders caused by both trauma [86], and biogenetics through epigenetic mechanisms.

CBT as a treatment is capable of inducing physiological changes analogous to chemical pharmacopeia. For example, in vivo imaging evidence demonstrates that the major abnormality in dopamine function in schizophrenia is located within the dorsal striatum, and currently, all licensed pharmacological treatments of schizophrenia affect the dopamine system [87]. Although some atypical antipsychotics may function through non-dopaminergic mechanisms, such as the serotonergic system, they all still bind to dopamine receptors. Behavioral therapy has been shown to be capable of altering dopaminergic signaling pathways similarly to pharmaceutical agents [88,89]. Likewise, the use of CBT for psychotic symptoms has been shown to decrease the stimulation of anger related regions of the brain (left inferior frontal gyrus and anterior insula) at a significantly greater rate than typical antipsychotics alone [90].

These examples provide the context for a greater role of behavioral therapy in treatment of psychotic symptoms. When combined with protocols for psychedelic-assisted therapy, behavioral therapy may have an even greater potential to provide symptom management or even therapeutic effects for psychotic

symptoms. Taking this into consideration, the broad exclusion of patients with psychotic symptoms from psychedelic-assisted therapy may represent a missed opportunity.

This study has collected and distilled the opinions and recommendations of the experts, who have come to the conclusion that trauma patients with psychotic symptoms do not always have to be excluded from psychedelic assisted therapy, however, if such treatment should be considered, it must be tailored to the population by providing extensive support and supportive psychotherapy. It may also be most safe and effective if participation is on an inpatient-basis. If psychedelic-assisted therapy is not conducted in a highly supportive context, exclusion is justifiable, however, to exclude people with all types of psychotic symptoms from all psychedelic treatment and studies may be unfounded. Overall, there is tremendous heterogeneity in psychotic experiences, and candidacy should be evaluated on an individual basis. With the right candidates and under the right conditions, trauma patients seeking/undergoing psychedelic assisted therapy who also have signs of psychotic symptoms may constitute a (pioneer) class of patients that could receive this treatment either as compassionate use or off-label patients.

Why Ask Experts

Interviewing experts was an effective strategy for gathering information around psychedelics and psychotic symptoms. No modern clinical studies have been conducted on the topic of expert beliefs regarding the effectiveness, safety, and risk of psychedelic-assisted psychotherapy for psychotic symptoms. This reflects a broader trend in psychiatry where clinical study populations are often unrepresentative of real-world patient diversity and severity. Mainstream opinion appears to be based on assumptions formed during the First Wave of Psychedelic Research, when an abundance of abuses were carried out on vulnerable hospitalized persons, often with chronic psychosis [1]. Today drugs ranging from PCP to LSD are still mischaracterized as being psychotomimetic (i.e., mimicking psychosis) leading some to believe psychedelics are contraindicated for this population. Empaneling a group of experts on psychedelics and psychiatry provides clinical perspectives grounded in experience and expertise which has provided more informed recommendations.

Expert Demographics

Out of the 12 conducted interviews, 9 of the experts were male (66%), while the remaining 3 were female (33%). In addition, 10 (84%) were White and 2 (16%) were people of color. Of the 12, 4 participants (33.3%) identified as sexual minorities. The White male dominant pool of participants is notable, and may be attributed to a confluence of interrelated factors including prestige, risk tolerance, racism, and sexism. The gender and racial imbalance within the field may also be due to the continuous presence of sexism, racism, as well as a myriad of challenges in the forms of lacking senior female mentors and familial commitments, which are readily discounted [91]. The imbalanced demographic profile may be further associated with the willingness to participate in risk-presenting studies and behaviors such as studying psychedelic research, which was both illegal and highly stigmatized until recently. Considering the aspects of legality towards the usage of psychedelics and patterns of risk-taking behavior among males,

we would predict a greater quantity of male experts being willing to participate in possibly stigmatizing interviews [92,93].

Targeting race demographics, where 84% of the interviewees identified as White directs us towards the officially acknowledged presence of structural racism in the field of Psychiatry (American Psychiatric Association, 2020). With only 3.3% of the psychiatrists [94] being Black, despite the 13.4% Black population in the U.S [95], the effects of historical as well as current racial discrimination seem apparent. The increasingly cascading factors of education disparities [96] and financial challenges [97], stacked on top of the racial biases, establish a social weapon, silencing the potential inspirations of the marginalized communities.

Alignment with Prevailing Approaches

Feedback from the experts demonstrated that while excluding individuals with psychotic symptoms from various psychedelic trials and treatment may be justified, this is not because psychedelics should be contraindicated for all cases of psychotic symptoms. Rather it is due to the fact that most studies and treatment contexts that exist today do not offer adequately supportive environments for such patients. Clinical trials are offered on an outpatient basis, and do not incorporate more extensive, personalized psychotherapy. They often select for patients with fewer comorbidities and milder illnesses, in order to minimize drop-outs. Nonetheless, expert participants believed that psychedelics could be beneficial to individuals with psychotic symptoms under the right conditions, demonstrating a departure with current assumptions by generalist and popular audiences.

Individuals with mental health conditions have historically not only been unable to access promising experimental treatment due to a variety of barriers [98] while also having been repeatedly subjected to inhumane experimentation [1]. Both of these have been true for psychedelic-assisted psychotherapy.

If equity is to be achieved, this must necessarily extend to individuals with mental health conditions being able to have access to experimental and promising psychedelic breakthrough treatments that are currently being demonstrated to be both highly efficacious and safe in clinical trials [98]. This is a matter of psychiatry advancing its ethics by taking a cue from other fields that have allowed patients access to innovative treatments such as experimental drugs for cancer and infectious diseases. While excluding some patients with some forms of psychotic symptoms from psychedelic research may be justifiable if their conditions would result in significant safety risk, excluding all individuals with psychotic symptoms is likely more reflective of inequities in psychiatric research rather than legitimate safety concerns. As data from the study indicated, there are individuals with symptoms of psychosis who would like to try psychedelic-assisted treatment, but are denied the opportunity. There are also those who, despite being denied access, use underground psychedelic treatment to their benefit or peril.

Next Steps in Investigating the Issue Further

More research must be done to create potential pathways for those with psychotic symptoms to benefit from psychedelics, and an initial pilot trial with loosened exclusion criteria around psychotic symptoms would be an ideal opportunity to gather more empirical data to support the hypotheses the experts suggested. This study would need to incorporate the various clinical recommendations given by the experts and proceed with caution by ensuring the proper safeguards are put in place. In addition, stratification by cause of psychotic symptoms (e.g., genetic, environmental) should be incorporated in any trial design. Individuals with a documented history of psychotic symptoms related to emotional experiences of trauma may be better candidates for inclusion than those who may have psychotic symptoms from other causes. Likewise, people with mild or transient psychotic symptoms might be better candidates than those persistent and severe symptoms. Targeting psychedelic treatment of underlying psychotic symptoms in conditions such as depression and PTSD may also provide insight into psychedelic mechanisms of actions of psychedelics more broadly.

Study Limitations

Study limitations include a non-random sampling of experts in psychedelics and psychiatry. The term “psychosis” has multiple layers of meaning due to its heterogeneity. As there is a spectrum or continuum of psychosis diagnoses with levels of severity, it was sometimes difficult to know whether the Experts were always referring to the same kind of psychotic symptom or disorder (i.e., brief psychosis, mild psychosis, chronic psychosis, psychotic features secondary to depression, transient psychotic symptoms associated with borderline personality disorder, etc.).

Another limitation is the lack of ethnic and racial diversity of participants. As we attempt to analyze the use of psychedelics while upholding demographic diversity among our participants, we stumble upon several physical and mental barriers. Specifically, one barrier while participating as a racialized person, is a stigmatizing social environment that discourages many from joining psychedelic studies as participants and researchers [7,8].

Conclusion

Experts agree that further studies must be done in order to determine how those with psychotic symptoms may benefit from psychedelic-assisted psychotherapy. That is to say, not everyone will respond the same, or even similarly, and outcomes depend on both variability at the individual, personality-level, as well as the way in which the psychotic symptoms developed. Some candidates may respond better, such as those who have a history of trauma, have psychotic symptoms that are secondary to a mood disorder, have symptoms that are less severe/chronic, who are open and interested in psychedelic medicine, who fulfill medical requirements, who are capable of forming a solid relationship with the therapist, and who are not actively paranoid or otherwise destabilized. Psychedelics are not contradicted for psychotic symptoms alone; rather a number of supports, precautions, and specific conditions are needed to safely and effectively provide psychedelic-assisted psychotherapy to people with symptoms of psychosis. In the end, perhaps the strongest indication that psychedelic-assisted

psychotherapy may prove to be safe and effective treatment options for some individuals with psychotic symptoms, in appropriate clinical contexts, is that such individuals have been active recipients and practitioners in traditional psychedelic practices in cultures around the world since time millennia.

Declarations

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Board of the University of Ottawa. The study was approved by an appropriate institution's ethics review board. All methods were performed in accordance with the relevant guidelines and regulations, including the Helsinki Declaration.

Consent for Publication

All authors and participants consent for the manuscript to be published.

Availability of Data and Materials

Due to privacy concerns and agreements surrounding confidentiality, raw datasets, transcripts or video-recordings obtained from anonymous experts cannot be shared. As per agreement with the interviewees, any data not included in the paper must remain private and is subject to deletion from any hardware or cloud-based storages upon the completion of the study.

Conflicts of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' Contributions

JL and MW contributed to the conception and design of the study. JL, MM, and KG wrote sections of the manuscript. JL and MM helped to transcribe and code data. All authors contributed to manuscript revision, read, and approved the submitted version.

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