

Should People With a History of Psychosis Be Included in Psychedelic Research?

Khaleel Rajwani

Volume 9, Number 2, 2026

URI: <https://id.erudit.org/iderudit/1124213ar>

DOI: <https://doi.org/10.7202/1124213ar>

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Publisher(s)

Programmes de bioéthique, École de santé publique de l'Université de Montréal

ISSN

2561-4665 (digital)

[Explore this journal](#)

Cite this article

Rajwani, K. (2026). Should People With a History of Psychosis Be Included in Psychedelic Research? *Canadian Journal of Bioethics / Revue canadienne de bioéthique*, 9(2), 118–134. <https://doi.org/10.7202/1124213ar>

Article abstract

The exclusion of all patients with a personal or family history of psychosis from psychedelic therapy research is a significant ethical concern. Beginning with a summary of the historical entanglement and disentanglement of psychedelic and psychosis research in Western psychiatry, I then discuss some of the important clinical and socio-cultural reasons why having a personal or family history of psychosis has become a standardized exclusion criterion in almost all contemporary research involving psychedelic drugs. While acknowledging that a high degree of caution is warranted, I contend that the exclusion of patients with a history of psychosis results in significant harms related to safety, accessibility, autonomy, and equity. Drawing on the paradigmatic case of the broad exclusion of pregnant people from drug research, I argue that, rather than preventing harmful consequences, a protectionist and exclusionary approach redistributes these harms in ethically problematic ways. People with a history of psychosis deserve equitable access to the benefits of psychedelic therapy research. Generating more robust safety data, dosage recommendations, and therapeutic guidelines for this group will improve clinical practice and reduce psychedelic-related harm broadly. I also explore the growing scientific literature that suggests novel psychedelic therapies could play a role in the treatment of psychosis, particularly in the case of negative symptoms of schizophrenia for which effective treatments are urgently needed. Ultimately, I critique the dominant practice of psychosis-related exclusion and defend the view that cautious clinical psychedelic research involving individuals with personal or family history of psychosis is ethically imperative. Adopting a more inclusive approach to psychedelic research would ultimately improve safety, increase access, reduce inequities, and prevent long-term harms caused by blanket exclusion.

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ARTICLE (ÉVALUÉ PAR LES PAIRS / PEER-REVIEWED)

Should People With a History of Psychosis Be Included in Psychedelic Research?

Khaleel Rajwani^a

Résumé

L'exclusion de tous les patients ayant des antécédents personnels ou familiaux de psychose de la recherche sur les thérapies psychédéliques soulève d'importantes questions éthiques. Après avoir résumé l'imbrication et la séparation historiques de la recherche sur les psychédéliques et la psychose dans la psychiatrie occidentale, j'aborde certaines des raisons cliniques et socioculturelles importantes pour lesquelles les antécédents personnels ou familiaux de psychose sont devenus un critère d'exclusion standardisé dans presque toutes les recherches contemporaines sur les psychédéliques. Tout en reconnaissant qu'une grande prudence s'impose, je soutiens que l'exclusion des patients ayant des antécédents de psychose entraîne des préjudices importants en matière de sécurité, d'accessibilité, d'autonomie et d'équité. En m'appuyant sur le cas paradigmatique de l'exclusion généralisée des personnes enceintes de la recherche sur les médicaments, je soutiens que, plutôt que de prévenir les conséquences néfastes, une approche protectionniste et exclusionniste redistribue ces préjudices d'une manière éthiquement problématique. Les personnes ayant des antécédents de psychose méritent un accès équitable aux avantages de la recherche sur les thérapies psychédéliques. La production de données plus solides sur la sécurité, de recommandations posologiques et de directives thérapeutiques pour ce groupe améliorera la pratique clinique et réduira de manière générale les préjudices liés aux psychédéliques. J'explore également la littérature scientifique croissante qui suggère que les nouvelles thérapies psychédéliques pourraient jouer un rôle dans le traitement de la psychose, en particulier dans le cas des symptômes négatifs de la schizophrénie pour lesquels des traitements efficaces sont nécessaires de toute urgence. Enfin, je critique la pratique dominante d'exclusion liée à la psychose et défends l'idée qu'il est éthiquement impératif de mener des recherches cliniques prudentes sur les psychédéliques impliquant des personnes ayant des antécédents personnels ou familiaux de psychose. L'adoption d'une approche plus inclusive de la recherche sur les psychédéliques permettrait en fin de compte d'améliorer la sécurité, d'accroître l'accès, de réduire les inégalités et de prévenir les dommages à long terme causés par l'exclusion généralisée.

Mots-clés

thérapie psychédélique, schizophrénie, psychose, bioéthique psychiatrique, éthique de la recherche, médicaments psychoactifs

Abstract

The exclusion of all patients with a personal or family history of psychosis from psychedelic therapy research is a significant ethical concern. Beginning with a summary of the historical entanglement and disentanglement of psychedelic and psychosis research in Western psychiatry, I then discuss some of the important clinical and socio-cultural reasons why having a personal or family history of psychosis has become a standardized exclusion criterion in almost all contemporary research involving psychedelic drugs. While acknowledging that a high degree of caution is warranted, I contend that the exclusion of patients with a history of psychosis results in significant harms related to safety, accessibility, autonomy, and equity. Drawing on the paradigmatic case of the broad exclusion of pregnant people from drug research, I argue that, rather than preventing harmful consequences, a protectionist and exclusionary approach redistributes these harms in ethically problematic ways. People with a history of psychosis deserve equitable access to the benefits of psychedelic therapy research. Generating more robust safety data, dosage recommendations, and therapeutic guidelines for this group will improve clinical practice and reduce psychedelic-related harm broadly. I also explore the growing scientific literature that suggests novel psychedelic therapies could play a role in the treatment of psychosis, particularly in the case of negative symptoms of schizophrenia for which effective treatments are urgently needed. Ultimately, I critique the dominant practice of psychosis-related exclusion and defend the view that cautious clinical psychedelic research involving individuals with personal or family history of psychosis is ethically imperative. Adopting a more inclusive approach to psychedelic research would ultimately improve safety, increase access, reduce inequities, and prevent long-term harms caused by blanket exclusion.

Keywords

psychedelic therapy, schizophrenia, psychosis, psychiatric bioethics, research ethics, psychoactive drugs

Affiliations

^a Department of Philosophy, McGill University, Montréal, Québec, Canada

Correspondance / Correspondence: Khaleel Rajwani, Khaleel.rajwani@mail.mcgill.ca

INTRODUCTION

Having a personal or familial history of psychosis¹ is one of the most common exclusion criteria in contemporary biomedical research involving psychedelic drugs. In this paper, I argue that the categorical exclusion of all patients with a personal or family history of psychosis from research into psychedelic therapies raises significant ethical concerns. I begin with an overview of the historical entanglement and disentanglement of psychedelic and psychosis research in Western psychiatry. I then survey and summarize the standard psychosis-related exclusion criteria incorporated in screening protocols for contemporary psychedelic therapy research. Several clinical justifications for these standardized criteria are examined, including the risk of adverse effects in this patient population, intensification of existing psychotic symptomology, hypersensitivity to persisting psychedelic-induced psychosis, and increased likelihood of long-term side effects including Hallucinogen Persisting Perception Disorder. Drawing on scientific literature and expert commentary, I acknowledge that these concerns warrant substantial precaution. However, I also contend that the prevailing perception of extreme risk in this patient group is likely amplified by historical propaganda, bias, stigma, and dated narratives linking psychedelic drugs with madness. Further, I consider the transcultural dimension of this ethical dialogue, noting that many indigenous cultures with living psychedelic practices have safely and meaningfully included people with lived experiences that may be categorized as psychotic in Western psychiatry. This perspective challenges the universality of current exclusionary frameworks in biomedical research and supports a transcultural approach to risk assessment and inclusion.

Next, the paper outlines the ethical implications of protectionist exclusion of patients with a history of psychosis from psychedelic research. First, blanket exclusion hinders the collection of qualitative and quantitative safety data that is relevant for clinicians prescribing psychedelic-assisted interventions in the real world. Many practical ethical issues are associated with excluding individuals who may be at higher risk of adverse effects related to psychedelics from clinical trials. Second, exclusion prevents certain individuals from accessing effective psychedelic-assisted interventions for treatment-resistant psychiatric disorders. It is plausible that the potential therapeutic benefits of evidence-based psychedelic therapies outweigh the risks for certain patients with a history of psychosis who are suffering from co-morbid diagnoses. Thirdly, blanket exclusion undermines autonomy by hindering the ability of people with a history of psychosis to weigh the risks and benefits of interventions and make informed decisions that could substantially affect their health. Fourth, psychosis-related exclusion has a direct negative effect on the participation of Black, indigenous, and racialized communities in psychedelic research. Marginalized people, including people with a history of psychosis, deserve equitable access to the potential benefits of innovative psychedelic research.

Drawing on the paradigmatic case of the exclusion of pregnant people from drug research, I argue that a paternalistic and exclusionary approach to psychedelic research does not prevent harmful consequences among a vulnerable population, but rather redistributes these harms temporally and demographically in morally problematic ways. Improving the evidence base by generating more robust dosage and safety data will have major long-term benefits for individual safety and autonomy, clinical practice, and public drug harm reduction. Blanket exclusion also forecloses the possibility of developing novel psychedelic therapies specifically targeted at schizophrenia and psychosis spectrum disorders. Emerging scientific literature suggests that psychedelic therapies could improve negative symptoms of psychosis, for which novel and effective treatments are urgently needed.

Ultimately, this paper critiques the dominant practice of psychosis-related exclusion and defends the view that inclusive and carefully supervised clinical psychedelic research involving individuals with personal or family history of psychosis is ethically imperative. A more inclusive approach to psychedelic research would improve safety, increase access, reduce inequities, and prevent long-term harms caused by protectionist exclusion.

PSYCHEDELICS & PSYCHOSIS: HISTORICAL ENTANGLEMENT AND DISENTANGLEMENT

Psychosis and psychedelic states of consciousness have long been entangled in the history of Western scientific and psychiatric discourse. In the early to mid-20th century, scientific discourses concerned with these two phenomena often overlapped, but research trajectories largely diverged in the aftermath of the 1960s US legal prohibition on psychedelic research (1). Despite this historical divergence, contemporary scientific interest in the overlap between psychedelic and psychosis phenomena has re-emerged in many disciplines, including clinical psychiatry, neuroscience, and psychopharmacology. Furthermore, interest in understanding psychedelic and psychosis as social, phenomenological, and pathological categories has re-emerged within contemporary critical discourses, including bioethics and madness studies, which critique the social stigmatization, pathologization, and ostracization of non-normative states of consciousness.

During the early to mid-20th century, “psychedelic” was just one term within a rich and contested taxonomy of psychoactive substances with the tendency to profoundly alter consciousness, perception of reality, cognitive functions, emotional experiences, and mood. Classic psychedelic drugs like psilocybin, mescaline, N,N-Dimethyltryptamine (DMT), and Lysergic acid Diethylamide (LSD) were also referred to as *psychotomimetic* (mimicking psychosis), *psychotogenic* (generating psychosis), *hallucinogenic* (generating hallucinations), and *psychodysleptic* (mind-disrupting) (1). These terms explicitly concretized perceived connections between consciousness-altering drugs and psychosis within prevailing social discourse. In the mid-20th century, leading researchers like Humphrey Osmond drew phenomenological comparisons between psychedelics and psychosis to develop models of madness and advance qualitative knowledge of hallucinatory phenomena. Comparative

¹ In what follows, the use of the term “history of psychosis” refers to “personal or familial history of psychosis”, unless specified otherwise.

research of that period included psychiatric studies as well as phenomenological analysis emerging from self-experimentation (1). Significant research took place using psychedelic drugs to understand and model psychosis, while clinical research investigated the use of psychedelics, particularly LSD, as a treatment for schizophrenia (2). As psychedelic drugs were introduced into psychiatric communities in the mid-20th century, an increasing number of clinicians and researchers argued that psychedelic therapy could be useful in the treatment of schizophrenia. Some also suggested that therapists should take LSD to help increase empathy with people experiencing schizophrenia (3,4).

However, the moral panic around psychedelic drugs in the 1960s led to the rapid closure of research programs around the world and marked a dramatic disentanglement of psychedelic and psychosis discourse (1). The proliferation of War on Drugs propaganda linking psychedelic drug use with madness coincided with a departure from scientific research and knowledge production that investigated psychedelic and psychosis experiences in parallel. Furthermore, the mid-20th century transformation of psychiatric discourse away from the dominant psychoanalytic paradigm, and towards biological and neuroscientific frameworks, meant that comparative phenomenological approaches were largely abandoned in favour of neurobiological and genetic research design (1).

Since the 21st century renaissance of research into psychedelic therapies in biomedicine, schizophrenia and psychosis have not been prominent therapeutic targets (2). However, some important neuroscientific and psychopharmacological research is ongoing. There is significant contemporary research interest in understanding the activation dynamics of serotonin receptors in the brain; decades of robust research have confirmed the historical speculation that changes in serotonin neurotransmission are important for understanding both psychedelic and psychotic experiences (5,6). As Geyer and Vollenwieder note, this agenda is closely linked with historical entanglements: “the fundamental idea that psychotic states seen in psychiatric disorders such as schizophrenia might be attributable, in part, to abnormalities in serotonergic systems began with the almost simultaneous discovery of lysergic acid diethylamide, psilocybin, and serotonin.” (6) Other topics of contemporary interest include the ways that antipsychotic drugs tend to block psychedelic experiences, similarities and differences between psychotic and psychedelic hallucinations, and the use of psychedelics in animal research to model and understand symptoms of psychosis (7-9). It is noteworthy that most contemporary scientific studies focus on using psychedelics to understand rather than treat psychosis.

Today, a broad range of psychedelic drugs are currently being investigated as part of innovative therapeutic interventions for mental illnesses such as post-traumatic stress disorder (PTSD), major depressive disorder, end-of-life anxiety, and substance use disorders. This includes classic psychedelics like psilocybin, LSD, DMT, and mescaline as well as non-classic psychedelics including ketamine, 3,4-Methylenedioxymethamphetamine (MDMA), and ibogaine.² As part of ongoing research, psychedelic drugs are generally prescribed and administered in a clinical setting under the supervision of trained therapists or healthcare professionals, and often as part of extensive psychotherapy.

Clinical trials involving psychedelic substances have been authorized by regulatory bodies in many global jurisdictions but remain at various stages of approval. Australia is the only country where MDMA and psilocybin have received regulatory approval as psychiatric medications for the treatment of treatment-resistant depression and PTSD. In the US, significant clinical research into psychedelic-assisted therapies is ongoing, but none have received regulatory approval; in a recent high-profile case, the US Food and Drug Administration rejected an application to approve MDMA-assisted therapy for the treatment of PTSD following phase 3 clinical trials (10). Other jurisdictions including Canada and some US states have increased access to therapeutic psychedelic use through compassionate access programs or decriminalization initiatives. In Oregon, Colorado, and New Mexico, psilocybin is legally accessible outside clinical settings through regulated adult use programs, and use is often supported by licensed facilitators.

PSYCHOSIS-RELATED EXCLUSION CRITERIA IN CONTEMPORARY PSYCHEDELIC RESEARCH

A personal or family history of psychosis is included as a criterion for exclusion from research when it is considered a comorbidity that could bias the results of the research or increase risk of adverse events (11). In contemporary psychedelic research, individuals with personal or family history of psychosis are generally excluded from clinical trials involving the administration of psychedelic substances as part of the therapeutic intervention (2). For example, in a study investigating psilocybin treatment of major depressive disorder with co-occurring alcohol use disorder at Johns Hopkins University the psychosis-related exclusion criteria were stated as follows:

- Current or past history of meeting DSM-5 criteria for schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition), or Bipolar I or II Disorder
- Have a first or second-degree relative with schizophrenia spectrum or other psychotic disorders (except substance/medication-induced or due to another medical condition)
- Has a psychiatric condition judged to be incompatible with establishment of rapport or safe exposure to psilocybin (12).

² Classic psychedelics are typically defined as substances that are partial agonists of 5-HT_{2A} receptors that produce substantially altered states of consciousness involving changes to affect, cognition, and perception. Non-classic psychedelics refer to substances which arguably share psychopharmacological and phenomenological similarities to classic psychedelics in certain dosages and contexts but may differ in their neurobiological mechanisms of action.

Similar or identical psychosis-related exclusion criteria were mentioned in my review of 115 actively recruiting clinical trials for psychedelic-assisted therapies on the US National Library of Medicine clinical trials database as of July 2024 (13).³ Psychosis-related exclusion criteria were specified in trials with psychedelic-assisted interventions targeted at PTSD, obsessive compulsive disorder, major depressive disorder, generalized anxiety disorder, substance use disorders, burnout among frontline healthcare workers, and depression in people with autism spectrum disorder, mild cognitive impairment, or Alzheimer's disease. These psychosis-related exclusion criteria were specified regardless of the psychedelic substance being administered as part of the intervention: the 115 studies surveyed included interventions with psilocybin, psilocin, ayahuasca, mescaline, ketamine, esketamine, MDMA, LSD and N,N-DMT. Psychosis-related exclusion criteria were also included in 44 studies accepting healthy volunteers. In some studies, exclusion criteria specifically mentioned major depressive disorder with psychotic features, antisocial personality disorder or borderline personality disorder. In other studies, exclusion criteria more broadly mentioned any personal history of a severe mental illness or psychiatric condition, which includes schizophrenia and psychosis spectrum disorders (13).

As of July 2024, there was a single study in the US National Library of Medicine database that did not include psychosis-related exclusion criteria: a proposed study investigating the tolerability of MDMA as a treatment for schizophrenia-associated asociality. This study was not yet recruiting as of July 2024, and will be discussed further in a later section. Although my review of exclusion criteria involved clinical trials registered in the US National Library of Medicine database, some of the trials included centres outside of the US. Psychedelic studies in other jurisdictions, including Canada and Australia, often include similar or identical psychosis-related exclusion criteria as studies based in the US.

WHY ARE PEOPLE WITH A HISTORY OF PSYCHOSIS EXCLUDED FROM PSYCHEDELIC RESEARCH?

Clinical Considerations

Given the psychoactive, hallucinogenic, and consciousness-altering properties of psychedelic drugs, and prevailing understandings of psychosis, caution around including individuals with a personal history of psychosis is intuitive and unsurprising. Common features of psychedelic experiences include hallucinations, delusions, dissociation, depersonalization, ego-reduction, among other changes in mood, cognition, and consciousness, which could subjectively overlap with common symptoms of psychosis. Clinical researchers have justifiable concerns about adverse effects in this patient population, particularly because psychedelics could plausibly intensify or exacerbate existing psychotic symptoms among those with active psychosis spectrum diagnoses. Past experiences or family history of psychosis could also increase the probability of adverse effects, challenging psychedelic experiences and bad trips, or signify hypersensitivity to long-term effects such as persisting psychedelic-induced psychosis or hallucinogen persisting perception disorder (HPPD). Considering these notable adverse effects, and the potential risks of compounding psychedelic experiences with psychosis experiences, precautionary exclusion of this group of individuals appears quite intuitive and sensible.

Even in otherwise healthy individuals, psychedelic drugs could precipitate drug-induced psychosis, which occurs when drug use triggers acute psychosis-like experiences or psychosis symptoms such as paranoia, delusions, and hallucinations. Sometimes these experiences are transient and sometimes they are lasting, and it may be initially difficult to discern psychedelic drug effects from psychosis symptoms. In perhaps the only published methodical survey on the topic, Malleson found episodes of psychedelic-induced psychosis were largely transient, and that examples of prolonged psychosis related to clinical LSD use were rare. In a survey of clinicians covering 50,000 LSD dosing sessions, he found that with clinical supervision the rate of psychotic reactions lasting greater than 48 hours was very low: 1.8 per 1000 patients and 0.8 per 1000 experimental participants (14).

Although there may be an intuitive association between psychedelic use and the intensification of psychosis symptoms, research is far from conclusive. A recent longitudinal study on the associations between psychedelic use and psychotic symptoms in the US and UK found no association between self-reported psychedelic use and a change in the number of psychotic symptoms within a two-month study period (15). Furthermore, psychedelic use was associated with a decrease in the number of psychotic symptoms in respondents with a personal history of psychosis (15). However, the researchers found an increase in psychosis symptoms associated with psychedelic use in people with a personal history of bipolar disorder, and a similar but weaker association with a family history of bipolar disorder (15). Another study of over 16,000 adolescent twins found that psychedelic use was associated with lower rates of psychotic symptoms when controlling for other drug use (16). Although we cannot conclude much due to the significant limitations of these methodologies, researchers in the field have suggested that more studies are warranted, and that psychedelics could exert less influence on psychosis symptoms in individuals with a personal or family history of psychosis than many speculate (15).

However, other researchers have observed that in some cases individuals who experience substance-induced psychosis go on to develop a persistent psychotic condition, such as schizophrenia spectrum disorder (17). According to a meta-analysis of 3 studies, the likelihood of transition from an episode of hallucinogen-induced psychosis to a diagnosis of schizophrenia was

³ Informal author-conducted search of the ClinicalTrials.gov registry (US National Library of Medicine) conducted in July 2024. The search reviewed 115 actively recruiting interventional studies investigating psychedelic or psychedelic-assisted therapies. Each study record was examined for exclusion criteria referencing schizophrenia or psychosis-spectrum disorders. This search was exploratory and not a systematic review.

roughly 26%, which was estimated to be higher transition rate than from opioid-, alcohol-, or sedative-induced psychosis, but lower than cannabis-induced psychosis (17). Researchers argued that there is a substantial risk of transition to schizophrenia from substance-induced psychosis related to hallucinogen use (17). Another study found that familial psychosis history predicted progression from substance-induced psychosis to schizophrenia (18). Of course, one difficulty of assessing this research involves understanding whether the individuals would have developed psychosis without psychedelic drug use, and whether a substance-related trigger is a central precipitating factor. Kendler et al. (18) suggested that “schizophrenia following substance-induced psychosis is likely a drug-precipitated disorder in highly vulnerable individuals, not a syndrome predominantly caused by drug exposure.” Transition from episodes of psychedelic-induced psychosis to long-term psychosis should be considered a risk of psychedelic use for people with a personal or family history of psychosis and must be factored into research ethics considerations and informed consent practices.

Some historical evidence shows that people with psychosis may have different dose sensitivity or altered dose response to a variety of psychoactive drugs, including psychedelics. For example, in one of the first documented trials of psychedelics in schizophrenia patients in 1947, researchers found that in schizophrenia patients, the onset of LSD experiences was delayed, and visual effects and euphoria were subdued compared to “nonpsychotic” participants.⁴ According to the researchers, psychedelic drug effects were generally experienced as different from underlying psychosis, and none of the patients experienced a worsening of their mental illness (2,19). Other studies in the mid-20th century confirmed a general need for higher doses of LSD than nonpsychotic patients to elicit psychedelic effects: certain psychedelic drug effects including euphoria, nausea, and headaches were found to be lower in patients diagnosed with schizophrenia (2,20). In another study, researchers administered LSD-25 to “paranoid” and “undifferentiated” patients with schizophrenia, as well as nonpsychotic participants and compared responses to a questionnaire about their subjective experiences. The study found that the patient group experiencing “undifferentiated” schizophrenia reported lesser subjective effects overall, while the responses of patients with paranoid schizophrenia, and baseline participants without psychosis, were qualitatively and quantitatively comparable (21). There are significant methodological limitations in analyzing historical research involving psychedelic use among individuals experiencing schizophrenia, particularly because studies before DSM III (1980) that reference schizophrenia or psychosis subtypes (e.g., paranoid, undifferentiated) are considered to have unreliable overlap with contemporary diagnostic criteria. However, these historical studies support the notion that certain patients with schizophrenia may react differently to psychedelics than patients without psychosis or healthy volunteers, including differences in dose sensitivity and differences in the subjective psychedelic-associated effects like euphoria (2).

Despite deeply held intuitions and practical consensus that people with a personal or family history of psychosis have substantially greater risks of adverse psychedelic effects, there is a notable lack of contemporary scientific literature investigating the risk profile of psychedelic use among this group. This knowledge gap is obviously exacerbated by widespread exclusion of this patient group from the renaissance of Western clinical psychedelic therapy research in the 21st century. However, some analysis of historical and contemporary evidence challenges widely-held beliefs about the severity of risks of psychedelic use for individuals with a history of psychosis — beliefs which often ground exclusion of this patient population from modern psychedelic research. A recent analysis of clinical research involving psychedelics and schizophrenia taking place from the 1950s prior to the prohibition of research in the early 1970s, noted that although psychedelics were occasionally destabilizing to individuals with schizophrenia, results were highly variable, and studies were conducted by practitioners who were not well-equipped to establish supportive therapeutic settings (4). Furthermore, the authors noted that despite the nearly unanimous view that psychedelics can destabilize or exacerbate schizophrenia, both historical accounts and current survey-based research include instances where psychedelics have been reported to have a beneficial impact on individuals with psychosis. Researchers hypothesize that psychedelic-induced increases in neural plasticity, changes in cognition, psychopharmacological effects, and supportive set and setting could all contribute to beneficial therapeutic effects. Researchers have argued that a low dose or a microdose of a classic psychedelic drug like psilocybin could be a viable treatment for the negative symptoms of schizophrenia, and that more neuroscientific and clinical research is warranted (4).

Complementing this assessment of historical data, recent population-level research has also contributed to the ongoing discussion regarding the risks of psychedelic use among individuals with psychosis-related risk factors. A retrospective analysis of emergency department (ED) data found an increased incidence of schizophrenia spectrum disorder among individuals who presented to the ED and had used hallucinogens in uncontrolled, non-clinical settings (22). However, the study had important limitations, including the broad definition of “hallucinogens” and the lack of specificity regarding the type, dose, and context of use. Despite these limitations, this data underscores the potential risks associated with unsupervised psychedelic use, particularly among those with psychiatric co-morbidities or psychosis-related risk factors, and supports the importance of generating more robust, context-sensitive safety data in controlled clinical research settings.

Although historical and contemporary literature indicates that people experiencing schizophrenia may experience different subjective effects or require different dosages to elicit psychedelic experiences, researchers have argued that the current literature does not indicate that schizophrenia patients are necessarily hypersensitive to classic hallucinogen-associated psychosis (2). Scholars have pointed to clinical observations and surveys of clinicians working with patients to argue against the notion that psychedelic use is highly likely to cause long-term schizophrenia (4). Researchers have also challenged the view that patients with a history of psychosis are more susceptible to the long-term negative effects of HPPD, a rare clinical

⁴ Studies cited from this era included terms like “nonpsychotic participant,” “undifferentiated schizophrenia,” and “paranoid schizophrenia,” which may be considered dated. These terms are emphasized with scare quotes when used for the first time in the paper to indicate dated, contested, or problematic nomenclature.

condition in which people who have used hallucinogenic drugs like psychedelics experience prolonged or re-occurring perceptual changes that are reminiscent of acute drug-induced effects (23). One preliminary study compared two groups of people with schizophrenia with prior LSD use: those who were diagnosed with HPPD, and those who were not. The study found no differences in socio-demographic or clinical characteristics between the HPPD and non-HPPD groups (24). However, researchers concluded that “very little is known about the co-occurrence of schizophrenia and HPPD or the associated clinical implications” and that further research is needed (24).

In the absence of robust scientific data and clinical evidence, consulting credible experts in scientific, clinical, and ethical fields is an essential resource for assessing the practical risks of including people with a history of psychosis in psychedelic-assisted therapy research. In a recent project on the topic of psychedelic-assisted therapy for people with psychopathological psychotic experiences and psychotic disorders, La Torre et al. (25) consulted the opinions of experts in the fields of psychiatry, clinical psychology, medicine, and psychedelic drug use. The experts highlighted the complex clinical expertise and institutional resources required for supporting people with a history of psychosis in psychedelic therapy contexts, but ultimately found consensus that while the exclusion criteria may be justified for psychedelic protocols that provide minimal psychological support, psychedelic-assisted psychotherapy is not necessarily contraindicated for all individuals within this group (25). Their analysis suggested that offering psychedelic-assisted psychotherapy under the right conditions could potentially benefit people experiencing psychosis-related conditions (25). The experts stressed the need for more research related to risks, safety, and identifying critical factors for predicting treatment outcomes, including specific symptomology, duration of the illness, symptom severity, quality of therapist-client relationship, role of trauma in mental illness, and the quality of other supportive structures in the client’s life (25). Yet, these important forms of research and knowledge production are exceedingly difficult or impossible today, given the blanket exclusion of people with psychosis from clinical psychedelic research.

Historical Narratives

Widespread concern around the risks of psychotic reactions to psychedelic drugs may be even more pronounced given historical narratives linking psychedelics with highly stigmatized accounts of psychosis and madness in the mid to late-20th century. Psychedelic researchers have argued that despite real possibilities of severe adverse effects, in general, “concerns about psychedelic use seem to have been based on media sensationalism, lack of information and cultural biases, rather than evidence-based harm assessments” (26). Furthermore, pervasive War on Drugs propaganda (disseminated primarily in the US) characterized psychedelic drugs as highly likely to lead to psychosis, madness, violence, and suicide in order to justify criminalization and political repression. Even as scientific discourses on psychedelic and psychosis phenomena disentangled, the connection between psychedelics and madness has maintained a deep influence within public opinion, biomedical research, psychiatric practice, and madness discourse.

The belief that LSD and other psychedelics frequently induce psychosis persists widely today. However, contemporary comparative research on psychedelics and psychosis has largely diverged from these outdated associations and overly simplistic views. For example, recent research demonstrates the highly complex differential neurophenomenology of hallucinations related to psychedelics and hallucinations on the schizophrenia spectrum, revealing a relationship that is far more nuanced and complicated than accounted for in historical models (27). Although, there is much less interest today in using LSD to model psychosis in research, the notion that psychedelic drugs provoke experiences of psychosis remains a factor for the persisting association between psychedelics and psychosis within clinical and social discourse. As Friesen argues, modern psychedelic research often seeks to rebrand by distancing itself from the stigmatized links between psychedelic drug use and madness, and the anti-establishment politics that were historically associated with psychedelic-using communities (1).

The scientific, medical, and bioethical community should be skeptical of any assertions made about links between psychedelic use and lasting psychiatric and psychotic effects without substantial evidence (26). The fact that both psychosis and psychedelic use are statistically prevalent in the population, and further, that the onset period of both typically occurs in early adulthood, may lead to mistaken causal inferences (26). It is also important to note that adverse effects, negative outcomes, and challenging experiences related to psychedelic use are relatively common even in patients without a history of psychosis. Furthermore, many people may attribute psychiatric and psychosis symptoms to the use of psychedelics drugs due to their striking and transformative subjective effects (26). The influence of War on Drugs propaganda campaigns linking psychedelic drugs with psychotic episodes may also lead to significant bias on the part of mental health professionals and policy makers.

Regulation and Research Ethics Oversight

In general, some instances of exclusion are rooted in regulatory or legal requirements, while others emerge through a culture of risk aversion within research design and research ethics review that often does not calibrate protectionist inclinations with real levels of risk (28,29). Psychosis-related exclusion from psychedelic research may be a regulatory requirement in specific legal contexts or certain jurisdictions, but in many instances, it falls in the latter category as a *de facto* form of exclusion practiced by researchers and ethicists. Furthermore, central regulatory frameworks in the US governing Institutional Review Boards (IRBs) have undergone very little revision or reform, despite bioethical consensus around the problems with protectionism and the importance of including marginalized communities in research. This often leaves IRBs to make decisions about inclusion and exclusion on a case-by-case basis (28).

Both de jure and de facto protectionism within contemporary research ethics largely emerged in response to high profile instances of unethical experimentation and human rights abuses involving vulnerable populations (28,30). Given the particularly disturbing histories of unethical, abusive, and exploitative experimentation throughout the history of Western psychedelic research, groups perceived as vulnerable or marginalized are likely to be subjected to a higher degree of caution, paternalism, and exclusion in contemporary research ethics review, including incarcerated people, people with a history of psychosis, and adolescents (31,32). However, emerging critiques within bioethics have challenged and problematized the concept of vulnerability, particularly as a justification for excluding entire populations from research (28). Scholars have argued that vulnerability is not a fixed trait but a context-dependent reality that may arise from various causes, such as impaired decision-making, social disadvantage, or situational coercion (28). These different forms of vulnerability require distinct ethical responses rather than blanket exclusion, and contemporary bioethical practice demands nuanced, context-sensitive approaches to vulnerability in research ethics that safeguard participants without perpetuating paternalism or undermining autonomy.

People with psychosis may be considered to have impaired capacity to consent to experimental interventions, particularly at higher levels of severity of psychosis. Research ethics review may take this into account, and there are already significant concerns and ongoing debates surrounding the ethics of informed consent in psychedelic therapy contexts (33-36). These ethical issues surrounding autonomy, consent, and caregiving in psychedelic research may be even more complex within the context of pathologies which deeply affect self-identity, which may include psychosis-related pathologies, as well as Alzheimer's and related dementias (37). The novel ethical issues and complexities posed by contemporary psychedelic research, as well as lack of time and material resources dedicated to the relatively new field of psychedelic ethics, can lead to further precautionary or protectionist exclusion by IRBs and other research ethics institutions (28)⁵.

Resource Allocation

Even when an individual's history of psychosis is not a direct contraindication for a specific psychedelic intervention, healthcare institutions or therapy centres may not offer adequately supportive environments for individuals with psychosis-related diagnosis, psychotic symptoms, or complex co-morbidities. Due to systemic underfunding of mental health services and a lack of resources in many psychiatric and mental health institutions, individuals with a history of psychosis may not receive the care, support, attention, and resources that they need and deserve during the course of psychedelic therapy research. Experts have argued that psychosis-related exclusion criteria could be ethically warranted for psychedelic-assisted therapy protocols that provide limited psychological support for participants (25).

In the US and other global jurisdictions with significant profit incentives for drug development, there is little incentive for pharmaceutical companies to conduct trials in groups perceived as higher risk; this is true not just of psychedelic research, but of drug research more broadly (38). Incentives to include higher risk groups will decrease even further once psychedelic medicines move beyond clinical trials and are approved by regulatory bodies for clinical use (38).

Cultural Norms

Definitions of psychosis and madness are culturally bound. The categorization and pathologization of non-normative forms of consciousness reflects dominant colonial and biomedical power structures. In their discussion of the topic of psychosis-related exclusion from psychedelic research, La Torre et al. (25) emphasize the importance of accounting for the relationship between psychedelics and psychosis not only within the context of Western psychedelic research, but also in the context of living psychedelic traditions with histories and practices in Indigenous societies going back millennia. Western frameworks for understanding both psychedelics and psychosis are heavily influenced by historical and cultural context, and biomedical psychedelic therapy is largely indebted to the history of Indigenous psychedelic healing practices (39). Thus, engaging with these contexts and knowledge systems is an important tool for deconstructing exclusion and stigma in psychedelic and psychosis research. Furthermore, the preferential treatment of Western scientific and ethical frameworks reinforces colonial bias and perpetuates the oppression of Indigenous practices, knowledge systems, and worldviews (40,41).

In many Indigenous communities with rich shamanic traditions, such as those in the Amazon basin and Siberia, experiences and phenomenologies that may be categorized in Western psychiatry as psychotic are not necessarily pathologized or stigmatized. Instead, individuals who hallucinate are often considered epistemically privileged and endowed with spiritual abilities that make them well-suited to participate in psychedelic rituals, or even uniquely situated to take on the role of a shaman or healer in their communities (25,42,43). While this does not establish that psychedelics are safe for all individuals with psychosis, it supports the idea that some people with psychotic experiences may benefit, or may not be adversely affected, by psychedelic use (25).

The risks of psychedelic use among people within psychosis-related diagnostic categories in Western psychiatry may be different and even amplified — but these risks are not well understood or documented. Furthermore, psychedelic use in clinical settings has a radically different safety calculus than non-medical or unsupervised use: active biomedical supervision, specific psychotherapeutic practices, and other safety and accountability measures, can substantially reduce the risk of adverse effects and improve positive outcomes (2,14). Growing bodies of scientific, social scientific, and bioethical literature emphasize the

⁵ For an overview of some of the key issues in contemporary psychedelic ethics see The Hopkins-Oxford Psychedelics Ethics (HOPE) Working Group Consensus Statement (36).

role of set and setting context in both psychotic and psychedelic experiences, which may play a significant role in reducing the likelihood of adverse events and orienting psychedelic-assisted interventions towards positive clinical outcomes (44-47). While sound research design, informed consent practices, and ethical oversight are essential to all research involving people with a history of psychosis, it is reasonable to hold that investigating psychedelic-assisted interventions in this group is not automatically unsafe in all cases.

THE HARMS OF PROTECTIONIST EXCLUSION OF PEOPLE WITH A HISTORY OF PSYCHOSIS

The exclusion of individuals with a history of psychosis from psychedelic research is often motivated by a legitimate concern for minimizing harm in the context of novel and potent therapeutic agents. Schizophrenia spectrum disorders are often chronic and persistent conditions, and the possibility that psychedelic use could trigger onset or exacerbate existing symptoms represents a serious concern. Thus, many clinicians, researchers, and ethicists adopt a risk-averse stance, guided by a desire to avoid unnecessary harm, particularly in early-phase trials where long-term safety data is limited. This cautionary approach reflects a broader ethos of protection within biomedical research, especially when working with populations that may be at elevated risk of negative consequences.

A personal or family history of psychosis can be an important risk factor for consideration in psychedelic research participation. It also may be an important exclusion criterion for sound observation and data collection within specific study designs. However, while scientists, clinicians, and ethicists will reasonably disagree on whether exclusion is justified in particular cases, effective critical bioethical inquiry demands that we question the broader ethical implications of dominant protectionist approaches and exclusionary practices.

As Friesen et al. note, the protection-inclusion dilemma faced by modern research ethicists inevitably involves difficult tensions between protecting potential participants from research-related harms and including under-represented or marginalized groups in research (28). Blanket exclusion can be ethically justified when the risks of an intervention are demonstrably significant and benefits are highly unlikely. Yet this is incredibly hard to establish when the risks of researching a drug are largely unknown, or when the research offers potentially intangible or unquantifiable benefits to current and future members of a population group. Friesen et al. argue that “while protectionism within research ethics stems from an important recognition of the harms that can befall certain individuals or populations as a consequence of research, over-protection, especially when it takes the form of exclusion from research, can lead to significant negative consequences as well.” (28).

For example, a growing body of critical bioethical literature has argued that the near-universal exclusion of pregnant people⁶ from most forms of pharmacological research leads to significant and widespread ethical harms (48). The dominant and standardized practice of excluding pregnant people, which is often an unquestioned insertion in the development of study participation criteria, may not cause immediate issues, and may even reduce the likelihood of harm in the near term. However, this exclusionary practice, grounded in a protectionist approach, has resulted in widespread harms to pregnant people in healthcare related to safety, access to medication, informed decision-making, and health equity that have persisted for decades (48). Because of their historical exclusion, pregnant people have limited knowledge about drug toxicity and dosing, thereby reducing their knowledge and putting them at greater risk. Pregnant people may also be discouraged from accessing beneficial medications due to unknown risks, and further, off-label medication use exposes them to risk without the safeguards or disclosure practices of clinical trials.

Pregnant people have thus been harmed by protectionist practices, and the systematic exclusion of pregnant people from research is not ethically defensible (48). In many historical cases, research protocols unjustly excluded women of childbearing age who were treated as always “potentially pregnant”. The harms precipitated by near-universal exclusion continue to affect pregnant people today and will continue to cause harm to this group well into the future, even as bioethical critique advances and inclusive pregnancy-related research programs evolve. Ethical parallels also persist across research contexts; for example, analogous concerns about the harms of protectionism have been raised by ethicists and advocates in the context of adolescents and people with disabilities being excluded from research (31,49).

A high degree of caution in the study of any novel drug-assisted intervention is warranted. However, the paradigmatic case of excluding pregnant people from drug research demonstrates the broader ethical issues with acting on seemingly reasonable intuitions in ways that can lead to harmful long-term consequences. By surveying some of the most significant harms of protectionist exclusion in the case of people with a history of psychosis, the practical parallels between the case of pregnancy- and psychosis-related exclusion from drug research become clearer. Ultimately, this approach clarifies the ways that people with a history of psychosis are in fact substantively affected by exclusion.

Safety

Excluding people with a personal or family history of psychosis from psychedelic research is ethically problematic in many significant ways. Firstly, blanket exclusion prevents the collection of important safety data related to therapeutic psychedelic use among this group. Modern scientific inquiry into psychedelic therapies to date has largely been based on data from highly

⁶ I have chosen to use the term “pregnant people,” a gender-neutral term which includes women and people of other gender identities that can or do experience pregnancy. I note that the vast majority of pregnant people discussed in the context of this paper identify as women, and I acknowledge the diversity of views around using gendered terminology related to pregnancy within academic scholarship.

screened populations and excludes many individuals and communities that may bear increased risks of adverse outcomes (38). Appelbaum argues that although “it seems prudent to exclude people with personal histories of psychosis and mania from trials of a drug that mimics the symptoms of psychosis ... in the real world of psychiatric treatment, people with [these diagnoses] that would have excluded them from the psilocybin trial are common [among psychiatric patients]” (38). Without a developed understanding of the complex safety profile for patients with a history of psychosis before psychedelics receive regulatory approval, psychiatrists will be left in the dark when psychedelic-assisted therapeutic tools are considered within complex practical clinical scenarios (38). Furthermore, the ethical urgency of modifying exclusion criteria is particularly time-sensitive, because once psychedelic therapies receive regulatory approval for clinical use, pharmaceutical companies will be far less likely to fund clinical trials involving groups perceived as high-risk (38).

Returning to the case of pregnancy-related research exclusion, scholars have noted that despite broad criticism from ethicists and international research bodies, data on the safety and efficacy of medications in pregnant people continues to be predominantly generated in post-marketing contexts rather than during clinical trials (48). Of course, all unstudied drugs have potential risk for adverse outcomes, particularly related to pregnancy, and critics often point to tragic cases like thalidomide and diethylstilbestrol (DES) which had devastating side effects on maternal and fetal health, including miscarriages, severe birth defects, and infant mortality. However, thalidomide and DES were not studied in controlled trials in pregnant populations prior to their approval, and because safety concerns were identified only after widespread use, the resulting harms affected a much larger number of people (48). This argument is generalizable to many cases of blanket research exclusion, including the exclusion of people with a history of psychosis from psychedelic research. Once approved for certain applications, psychedelic interventions are likely to be used off label in complex clinical situations, without any controlled safety data for this patient group. In the tragic case of thalidomide, the devastating consequences would have been much less widespread if safety trials had been conducted in small groups with well-established consent and disclosure processes (48). Similarly, if there are significant risks associated with certain psychedelic drugs in people with a history of psychosis, generating data and understanding within controlled research contexts can help contain and prevent wider harms.

There are two noteworthy disanalogies between these cases. Firstly, many people with a history of psychosis currently use psychedelic drugs in diverse non-medical settings. Furthermore, people with experiences that may be classified as psychotic have historically consumed psychedelic drugs across diverse Indigenous cultures for millennia. This was not the case with thalidomide or DES which were novel experimental drugs with no history of cultural, spiritual, or prior medical use. Secondly, in future contexts where psychedelic therapies are approved, a history of psychosis is likely to be included as a contraindication for many psychedelic-assisted interventions. However, inclusive research that can reduce psychedelic-related drug harm is still an important and ethically consequential benefit.

Recent developments in pregnancy-related research ethics offer promising examples of how research in historically excluded groups can be safely and effectively undertaken. In response to longstanding critiques of the exclusion of pregnant individuals from drug trials, researchers and ethicists have developed strategies that better balance precaution with inclusion. These include risk-tiered research models that prioritize initial safety assessments in non-pregnant populations before gradually expanding inclusion, the use of real-world evidence through observational registries, adaptive trial designs, and enhanced informed consent processes (50-52).

Drawing on these precedents, clinical psychedelic researchers can pursue analogous approaches to include individuals with a history of psychosis in studies, avoiding the long-term safety harms of exclusion. By critiquing and modifying strict exclusion criteria, the findings that emerge from psychedelic research will better reflect the practical clinical contexts in which psychedelic-assisted therapeutic interventions will be used. Inclusion of people with a history of psychosis in well-designed controlled clinical research with effective safeguards would improve knowledge about the safety and efficacy of psychedelic therapies and improve outcomes in the long run.

Accessibility

Blanket exclusion will continue to unjustly prevent certain individuals from accessing effective psychedelic-assisted interventions for other treatment-resistant psychiatric disorders, such as major depressive disorder and PTSD. As psychedelic-assisted interventions are destigmatized and more widely accepted in clinical practice, many patients with a personal or family history of psychosis will become interested in psychedelic-assisted treatments for a co-morbid psychiatric diagnosis (38). There is significant research demonstrating that patients with target diagnoses for novel psychedelic therapies are likely to have co-morbidities that would typically exclude them from psychedelic trials; for example, people with major depression are more likely to have a sibling with schizophrenia or bipolar disorder than the general public, are more likely to have attempted suicide, and are more likely to have borderline personality disorder, all of which could be contra-indicated for psychedelic therapies or match exclusion criteria for studies (38).

As psychedelic-assisted interventions gain regulatory approval and mainstream biomedical acceptance, patients with a history of psychosis who have been excluded from research may continue to be excluded from approved clinical interventions involving psychedelics.⁷ Without controlled safety data, patients with a personal or familial history of psychosis may be discouraged from accessing beneficial psychedelic-assisted interventions due to fears of unknown risks and adverse effects.

⁷ This may also apply to patients who have been excluded on the basis of past suicidality, bipolar disorder, or borderline personality disorder.

Even if this group is not excluded in clinical practice, these same patients may be exposed to unknown harms through off-label prescription without benefitting from the ethical safeguards and consistent health monitoring that are typical features of clinical trials (48).

As discussed, the view that including patients with a history of psychosis in these treatments would necessarily result in outsized risks for adverse events is not well demonstrated. Conversely, studies have shown some psychedelic interventions to be effective *despite* comorbidities. For example, MDMA-assisted psychotherapy for the treatment of PTSD was shown to be highly efficacious, even in patients with significant (non-psychosis) comorbidities (53,54). As new research findings and clinical knowledge emerge, it is plausible that the benefits of a novel psychedelic therapy targeted at a treatment-resistant diagnosis unrelated to psychosis will outweigh risks for patients with a history of psychosis even if the risks for the individual are considered elevated.

Autonomy

Protectionist exclusionary practices undermine autonomy by hindering the ability of people with a history of psychosis to weigh the risks and benefits of interventions and make informed decisions that could substantially affect their health. This applies both to autonomous individuals making an informed choice to participate in clinical research in a context of uncertainty, and for individuals in the future tasked with making decisions about pursuing approved psychedelic therapies as part of their healthcare.

Miller and Wertheimer argue that “hard” paternalism entails restricting the freedom of persons who are substantially autonomous to protect them from the potentially harmful consequences of their fully voluntary choices, without their consent (55). Completely preventing a particular group from freely consenting to experimental research thus constitutes a form of hard paternalism. In a practical ethical sense, hard paternalism appears to be ethically justified if there is strong evidence and expert consensus that (a) the risks of the action are substantial and (b) the decision-maker does not have the capacity to reasonably understand, assess, and consent to the risks. Today the scientific and clinical community lack the robust evidence and consensus demanded of criterion (a). And although there are complexities in assessing the capability of people with psychosis at increasing levels of severity to make informed decisions about experimental interventions (b), the ethical bar for establishing complete restrictions on free choice should be high. While many cases of psychedelic-assisted interventions involving people with a history of psychosis could meet this standard, and thus morally demand some form of paternalistic intervention like research exclusion, it is not evident that this paternalist and protectionist form of exclusion should be practiced universally across the incredibly wide spectrum of psychosis cases and clinical psychedelic interventions.

Let us imagine that after a robust set of studies, we find out that the risks of a MDMA-assisted therapy for PTSD are substantially higher for patients with a history of psychosis. Say for example that these participants are far more likely to experience acute adverse effects related to psychedelics than participants without a history of psychosis, and some experience a worsening of their psychosis symptoms, but the patients experience roughly the same positive long-term effects on PTSD outcomes. It does not follow that we *must* exclude these individuals from the therapy based on this additional risk factor. A specific clinical evaluation of the risks and benefits for an individual case will vary widely across diverse patients and differ based on the severity of the patient’s past and present mental illnesses, previous responses to treatments, past experiences with psychedelics, personal risk tolerance, therapeutic expectations, and accessibility of alternatives, among countless other clinical factors. Further, there are many other psychological and social factors that could increase individual risks for adverse effects and yet do not serve as a basis for exclusion. The threshold for acceptable or reasonable risk will vary greatly, and it should be up to patients, families, clinicians, and other relevant decision-makers to assess the specific risks of participating in a particular psychedelic-assisted intervention on a case-by-case basis — even when the risks may be substantially heightened for a particular patient with a history of psychosis.

Returning to the case of exclusion of pregnant people from pharmacological research, scholars have argued that blanket exclusion undermines autonomy by limiting the ability of the individual to assess the risks for themselves and decide if participation would be in their best interest (56). Additionally, the absence of robust evidence that has resulted from historical research exclusion creates barriers to making informed choices. This further undermines the autonomy of individuals from the excluded patient group who are tasked with making major decisions about their health (48). As Zur articulates: “it is not possible to properly weigh the risks and benefits and determine the option most in line with one’s values when information regarding these risks does not exist.” (48)

Decisions about psychedelic interventions for patients with comorbidities should not be made based on preconceived notions but should take into account established bodies of safety literature and considerations relevant to the specific therapeutic model, research design, and clinical delivery. Blanket exclusion can paternalistically halt the collection of data that illuminates the possible risks and benefits associated with psychedelic therapies — an important aspect for an *informed* consent process in dynamic and evolving clinical contexts. This ultimately prevent patients from making informed decisions about their own care. As empirical data about the risks emerges, it may be the case that specific and targeted precautionary exclusion of patients with a history of psychosis from particularly risky psychedelic-assisted therapies is justified. However, how to determine that threshold of risk is a difficult question that cannot be determined without an evaluative process grounded in patient-centred conversations and ethical consensus-building, backed up by more robust quantitative and qualitative data.

Diversity

Biomedical psychedelic research has systematically underrepresented racialized and Indigenous peoples, and research has largely neglected the complex role of racial trauma in psychopathology and the psychodynamics of psychedelic therapy (39,57). In an analysis of psychedelic studies conducted from 2000 to 2017, less than 6% of participants were racialized and less than 5% were Indigenous (39,57). Racialized and Indigenous peoples are more likely to be diagnosed with schizophrenia and psychosis spectrum disorders; for example, African American and Latin American individuals are diagnosed with psychosis spectrum disorders at rates 3 to 4 times higher than white Americans of European descent (25,58). As La Torre notes, psychosis-related exclusion in psychedelic-assisted psychotherapy has a direct impact on racialized and Indigenous communities' participation in psychedelic research (25).

Thus, racial injustice stemming from a lack of diversity in participation will be further exacerbated by broad exclusion of people with a history of psychosis. This significant ethical issue also applies to the exclusion of other diagnostic groups from psychedelic research, such as people with a history of bipolar disorder, which also correlates strongly with racialization and social marginalization. The systematic underrepresentation of racialized peoples in psychedelic research participation also casts doubt on whether psychedelic-assisted therapy evidence and theoretical frameworks are generalizable beyond a primarily white (male) European majority (39,57).

EQUITABLE DISTRIBUTION OF THE BENEFITS OF PSYCHEDELIC RESEARCH

Beyond extending harms, protectionist research exclusion is also an ethical failure when it contributes to an unjust distribution of healthcare research benefits between social groups in the long term (28). Exclusionary practices reduce participation and access but also hinder the possibility of developing novel therapies for people experiencing schizophrenia and psychosis spectrum disorders. The psychosis spectrum includes diagnostic categories with some of the most urgent need for innovative treatments, and yet people with a history of psychosis are largely excluded from the benefits of a new category of interventions that have been considered to have therapeutic promise for a range of applications for the treatment of psychosis symptomology and co-morbidities. Contemporary psychosis-related exclusion involves the entire spectrum of psychedelic interventions, which includes dozens of drugs with a wide range of possible clinical applications, psychopharmacological dynamics, and neurophenomenological nuances.

Novel Interventions for Schizophrenia and Psychosis Spectrum Disorders

The negative mental health outcomes of individuals diagnosed with schizophrenia and psychosis spectrum disorders represents a significant and ongoing public health crisis. Despite advances in psychiatric practice and mental health care in other domains, people with schizophrenia continue to face disproportionately poor outcomes, in terms of both morbidity and mortality. Individuals diagnosed with schizophrenia have a life expectancy of 20 years less than the general population, largely due to a combination of suicide (13 times more likely), high rates of cardiovascular disease, and other preventable physical health conditions; this gap has worsened in recent decades (59,60). The rate of sustained clinical or social improvement for people diagnosed with schizophrenia has remained stagnant for decades. Moreover, individuals with schizophrenia frequently experience social exclusion, unemployment, and homelessness, all of which exacerbate the challenges of managing the illness (61). This alarming crisis highlights the urgent need for more effective interventions and therapeutic models that benefit those living with schizophrenia and psychosis spectrum disorders.

In an influential review on the treatment of symptoms of schizophrenia, Correll and Schooler note that current antipsychotic treatments primarily target reducing the *positive* symptoms like auditory hallucinations, while the *negative* symptoms, like asociality and diminished expression, are more challenging to treat and constitute an unmet medical need for which new and effective treatments are urgently needed (62). Innovative and effective interventions for people with psychosis are ethically consequential and would greatly improve the quality-of-life of individuals and their families (4). Although effective interventions and standards of care exist, approved antipsychotic medications are associated with a range of therapeutic outcomes and can have significant adverse effects that vary among different patient groups and clinical contexts (4,63). There is a clear consensus around the need for action and innovation in the context of negative and treatment-resistant symptoms of psychosis; pharmacological developments and novel therapeutic interventions could substantively improve clinical outcomes and quality of life for many people with psychosis worldwide.

In a recent paper, Wolf et al. (2) argue that carefully considered research into psychedelic-assisted interventions has promising possibilities for the treatment of schizophrenia, grounded in sound psychopharmacological and neurophenomenological rationale. As mentioned above, expert analysis of historical research into psychedelic-assisted treatments for schizophrenia has already suggested that low-dose psychedelic administration could be an effective treatment for the negative symptoms of schizophrenia (4). Classic psychedelics are known for enhancing neural plasticity, which may have beneficial effects on a range of neuropsychiatric conditions, including schizophrenia and Alzheimer's and related dementias (2,4,37). The well-established neurogenic and synaptogenic properties of psychedelics, and the association between negative schizophrenia symptoms and cortical atrophy, could provide the foundations of a novel tool for treating schizophrenia (2). It is well established that 5HT-2A receptors mediate the psychedelic effects of classic psychedelic drugs, and these receptors are a key target in the treatment of depression, delusions, hallucinations, and other psychosis symptoms (2,27). It is reasonable to think that psychedelic psychopharmacology could play a role in the development of novel and efficacious pharmacological interventions

targeted at schizophrenia and psychosis spectrum disorders (2). Blanket exclusion from research and drug development prevents the possibility of further investigation into these therapeutic avenues.

Researchers and clinicians have specifically suggested that psychedelic interventions could help treat negative symptoms of schizophrenia and psychosis related to impaired social motivation or asociality. There are currently no accepted treatments for psychosis-related asociality, and impaired social motivation can radically reduce quality of life of people with psychosis-related diagnoses. Given the tendency for MDMA to increase social motivation, empathy, and bonding in healthy volunteers and participants in MDMA-assisted therapy, researchers from the University of California, Los Angeles, have proposed a study investigating the tolerability of MDMA in patients with schizophrenia. While antipsychotic medications can address many symptoms of schizophrenia, they are generally ineffective in treating deficits in social motivation which contribute to significant social impairment. Unlike traditional stimulants, MDMA enhances empathy, emotional closeness, and sensitivity to positive social cues, possibly due to its influence on oxytocin, a hormone linked to social bonding (64).

The researchers propose an exploratory model with safeguards, involving ascending dose administration over the trial period, which will be halted if patients experience increased psychotic symptoms. The researchers also propose exclusion criteria related to aggression or suicidality (64). This proposed study, with sound clinical and psychopharmacological rationale, expert clinical reasoning, and added safety precautions, reflects an ethics of cautious inclusion and tailored investigation that aligns with the inclusive bioethical approach that follows from the central argument of this paper. The results of the project would be a critical first step in understanding the safety profile of MDMA in patients with schizophrenia and setting MDMA dosage standards for future research in this patient group. Beyond this, the study will allow clinicians and researchers to better understand whether psychedelic compounds and psychedelic experiences could play an innovative role in addressing treatment-resistant social deficits related to schizophrenia and other psychiatric disorders.

Psychedelic-assisted interventions may also be a therapeutically useful tool for learning to navigate and process psychosis-related auditory and visual hallucinations. From a phenomenological perspective, both schizophrenia-related and psychedelic-induced hallucinations may be interpreted as experiences with spiritual or metaphysical meaning, despite significant etiological differences (27). Recent research on the connections between LSD, madness, and healing has suggested that the resemblance and shared mystical qualities of psychedelic and psychosis states of consciousness could offer tools for healing (65). Emerging literature suggests that the effects of psychedelic alterations to consciousness in supervised clinical settings would not necessarily overlap with, or worsen, everyday psychosis-related phenomenology. Despite the extremely vivid and immersive qualities of both psychedelic and psychotic hallucinations, people with psychosis using psychedelic drugs can typically distinguish between drug effects and everyday consciousness, and recognize sensory-perceptual changes as transient effects (27). Conversely, psychotic hallucinations tend to be reported as persistent over weeks or months, unpredictable, and harder to differentiate from everyday perception (27).

There may also be specific therapeutic effects associated with psychedelic experiences. Some studies of the mid-20th century using LSD in psychiatric patients with schizophrenia found that participation in group therapy increased while on LSD, and patients exhibited more positive social and emotional behaviour during psychedelic-assisted sessions than during placebo sessions. Participants also experienced other forms of positive affect and psychotherapeutic progress (66). Although no consensus on the therapeutic effects of psychedelics emerged in early studies of psychedelics in people with psychosis during the 1940s and 1950s, participants were generally all institutionalized patients in Europe and studies generally only administered LSD (2). Contemporary psychedelic research involves similar demographic and geographic limitations, which poses significant problems for generalizing negative or positive findings (67).

Psychedelic-assisted interventions targeted at psychosis spectrum disorders are likely to emerge in the mainstream model of psychedelic-assisted psychotherapy. When used in conjunction with evidence-based psychotherapeutic techniques and beneficial set and setting construction, the effects of psychedelic drugs could contribute to long-term decreases in psychiatric symptoms and improved quality of life, including altered self-perception, increased introspection, positive mood changes, and improvements in personality traits such as openness and empathy (68-71). However, other neuropharmacological and therapeutic models, including psycholytic, microdosing, and neuromodulation models, are worthy of preclinical and clinical research consideration as part of developing novel psychedelic-assisted treatments targeted at people with schizophrenia and other psychosis spectrum disorders (2).

Harm Reduction

While biomedical and bioethics scholarship largely focuses on clinical psychedelic-assisted interventions for individuals with specific psychiatric diagnoses, the vast majority of global psychedelic use takes place in non-clinical settings. This includes religious and cultural use, legal, decriminalized and criminalized non-medical use, as well as retreats and unregulated therapeutic use. Legal access to psychedelic therapy is rare and inequitable, and most psychedelic drugs remain controlled and criminalized worldwide. Given their exclusion from clinical research, people with a history of psychosis almost exclusively use psychedelic drugs in unsupervised and unregulated settings, for diverse reasons.

Harm reduction approaches focus on minimizing negative consequences of drug use, and promoting dignity, autonomy, and informed decision-making (72). Research investigating safety, dosage, and effects on psychosis-related symptoms is therefore critical for psychedelic drug harm reduction. Evidence-based harm reduction has been widely adopted in bioethics,

psychotherapy, and public health initiatives as a compassionate and ethical response to potentially risky behaviours like drug use and sexual activity (72).

In the short term, generating evidence on psychosis-related risks of psychedelic use will support individuals making decisions about psychedelic use, as well as therapists, facilitators, and first responders. Such research will also enhance transdiagnostic harm reduction models like the Psychedelics Harm Reduction and Integration model, which focuses on reducing harm among people using psychedelic substances in ceremonies, festivals, and underground therapy (73). Specific data on dosage and safety for people with a history of psychosis can also inform public health initiatives such as labels, warnings, and informational pamphlets in places with legal access to psychedelics. For example, cannabis labelling in Canada includes specific psychosis-related risk information because of research programs investigating the risks of cannabis consumption by people with a personal or family history of schizophrenia. Similar safety research into psilocybin and other psychedelics would substantially improve public health regulation and education in a growing number of jurisdictions with legal psychedelic drug dispensing.

FUTURE CONSIDERATIONS AND CONCLUSIONS

The development of clinical psychedelic therapies for people with a history of psychosis is interesting, controversial, and highly challenging. Due to widely held beliefs and assumptions about both psychedelics and psychosis, individuals with a history of psychosis, who are already marginalized in many ways, are often subject to protectionist exclusionary practices, and are unjustly denied access to equitable consideration within psychedelic research and discourse. People with present, past, or family history of psychosis deserve to be a part of the rapidly unfolding contemporary psychedelic therapy discourse. They deserve to benefit equitably from psychedelic-related research and innovation. Increasing the participation of people with a history of psychosis in psychedelic research is ethically important for current and future populations. Advocating for inclusion of people with a history of psychosis in contemporary psychedelic therapy discourse also adds to emerging literature that seeks to productively rebuild the historical bridge between psychedelic and psychosis discourse that largely deteriorated in the late 20th century (1).

In the complex context of psychedelic therapy research, developing a cautious inclusive approach is not as simple as lifting standardized exclusion criteria writ large. There are clearly substantial risks associated with psychedelic use among people with a history of psychosis, and not all people in this group will be suitable candidates for psychedelic-assisted interventions. However, in parallel with modern bioethics and social justice movements which advocate for more inclusion of marginalized groups within drug research, critically inspecting exclusion criteria, study methodologies, research ethics practices, and clinical frameworks will ultimately support autonomy, improve safety, and advance equitable access to the benefits of psychedelic research (48).

Initially, people with a personal or familial history of psychosis, but no active diagnosis, should be seriously considered for psychedelic-assisted interventions that could effectively address their existing mental illnesses. As neuroscientific and clinical research progresses, people with active psychosis-related diagnosis could be considered for inclusion in psychedelic therapies that target co-morbidities, as well as novel research that could substantiate innovative interventions for psychosis-related symptomatology. Frameworks for increasing the participation of pregnant individuals in research, such as risk-tiered models, observational studies, and enhanced consent, show how the historically excluded populations can be included safely and responsibly in research. Psychedelic researchers should adopt similar approaches to include individuals with a history of psychosis, avoiding the long-term harms of blanket exclusion. Clinical case series, case-controlled studies, cohort studies, and population level investigations pose little or no health risk to participants but can generate more knowledge about the intersection between psychedelic use and psychosis-related risks.

There will inevitably be specific risks, both known and unknown, that must be addressed in depth as part of an ethical informed consent process for people with a history of psychosis wishing to participate in psychedelic therapy research. The question of how best to address unknown risks within informed consent practices is already an important conversation within psychedelic ethics but requires deeper bioethical inquiry and empirical research. A more inclusive approach to psychedelic research involving people with a history of psychosis also demands generating interdisciplinary expert consensus and developing research ethics frameworks that specify clinical ethical rationales for exclusion and shift the burden of proof towards justifying exclusion.

As research develops along this new frontier, there are further ethical concerns and considerations that will undoubtedly emerge. Patient autonomy in the context of psychosis ethics and madness discourse is an ethically complex issue, particularly in cases involving non-consensual institutionalization, and cases involving psychoactive drug use. Ethicists and clinicians have argued that the consent process for psychedelic-assisted therapies, which involve potentially transformative and ineffable experiences, as well as states of intense vulnerability, should be enhanced in ways that attend to the important differences between psychedelic-assisted and other kinds of interventions (33). In their recent work, Peterson et al. (37) flag important ethical considerations for psychedelic medicine research in the context of Alzheimer's disease and related dementias, which may have important similarities with the context of psychosis. One of the most important analogous ethical considerations involves the complexities of understanding how psychedelic experiences like "ego dissolution" can affect a person's experience of selfhood, particularly when both pathologies and psychedelic experiences can involve radical alterations in self-perception and self-processing. Other important parallels include age-related vulnerability and the potential exploitation of patient desperation (36). Furthermore, given the alarming history of flagrant unethical experimentation on institutionalized patients in

20th century psychedelic research, there is a magnified ethical gravity surrounding issues of agency, autonomy and consent involving institutionalized people with Alzheimer's and related dementias or psychosis spectrum disorders. Contexts involving people with psychosis or dementia also demand deep ethical consideration of how psychedelic-assisted therapies might influence the complex dynamics of caregiving (37).

A critical approach to bioethical inquiry is important in this case, given the historical mistreatment and abuse of people with lived experiences of psychosis in Western biomedical contexts, and intense social stigma compounded by broader social inequity and intersecting forms of oppression. Although this paper has briefly reflected on cultural norms and impacts of psychosis-related exclusion on diversity, much more must be said about the underexamined social consequences of exclusionary practices in biomedical psychedelic research.

Including people with a history of psychosis in clinical psychedelic research will have important long-term benefits for knowledge production, therapeutic care, and healthcare justice. Responsible and inclusive research will improve safety, increase access, reduce inequities, and prevent long-term harms associated with blanket exclusion. Deeper investigation into the relationship between psychedelics and psychosis has the potential to decrease drug-related harm, enhance autonomy, expand access to effective interventions for co-morbid mental illnesses, and substantiate novel treatments that could improve clinical outcomes and quality of life for countless people.

Table 1. Key Takeaways

Research Exclusion	<ul style="list-style-type: none"> Blanket exclusion of individuals with personal or family history of psychosis from psychedelic research is ethically problematic and perpetuates harms that parallel other cases of research exclusion.
Historical Context	<ul style="list-style-type: none"> Exclusionary practices are shaped by historical propaganda linking psychedelic drug use with madness and psychosis. Critical review of this historical legacy is imperative.
Regulatory Oversight	<ul style="list-style-type: none"> Many researchers and ethicists exclude people with psychosis as a standardized criteria in psychedelic research. Ethical review should include justification for exclusion, rather than assuming it as default.
Risk Assessment	<ul style="list-style-type: none"> While specific clinical risks exist, actual evidence is limited. Intuitions may be based on outdated or biased assumptions. Case-by-case evaluation of research is warranted.
Protectionist Harms	<ul style="list-style-type: none"> Overprotection can cause significant long-term harms, such as in the case of excluding pregnant people from drug trials. Inclusivity, with due caution and safeguards, aligns with a critical bioethical approach.
Safety	<ul style="list-style-type: none"> Exclusion prevents collection of critical safety and dosage data. Without research, future off-label or unsupervised use may pose greater harms.
Autonomy	<ul style="list-style-type: none"> Exclusion undermines patient autonomy and informed consent. People with decision-making capacity should be allowed to make an informed assessment about research participation and risks. Lack of evidence further hinders informed decision-making in this population group in future clinical contexts.
Access & Justice	<ul style="list-style-type: none"> Exclusion reduces access to promising therapies for co-morbid or treatment-resistant conditions. Racialized and Indigenous communities are disproportionately affected by exclusion due to diagnostic disparities. All people deserve equitable access to the benefits of psychedelic therapy research.
Cultural Sensitivity	<ul style="list-style-type: none"> Many cultures with psychedelic practices have safely included people with experiences that may be considered psychotic or pathological within Western psychiatric frameworks. Risk assessments should consider cultural context and transcultural safety evidence.
Therapeutic Potential	<ul style="list-style-type: none"> Emerging literature suggests that psychedelic therapies have promise for treating negative symptoms of schizophrenia. Carefully designed studies could lead to novel therapeutic interventions for people with treatment-resistant psychosis spectrum disorders.

Reçu/Received: 06/03/2025

Remerciements

Je remercie Ian Gold et Phoebe Friesen pour leurs commentaires sur les versions préliminaires de cet article. Je remercie les participants au Sommet Hopkins-Oxford sur l'éthique des psychédéliques de 2024, qui ont posé des questions pertinentes et offert des retours constructifs pour ce projet. Je reconnais les contributions pérennes des peuples et des communautés autochtones à la connaissance des médecines psychédéliques, sans lesquelles mes travaux n'auraient pas été possibles.

Conflicts d'intérêts

Aucun à déclarer

Publié/Published: 16/03/2025

Acknowledgements

Thank you to Ian Gold and Phoebe Friesen for their feedback on drafts of this paper. Thank you to participants of the 2024 Hopkins-Oxford Psychedelic Ethics Summit who asked helpful questions and provided constructive feedback for this project. I acknowledge the longstanding contributions of Indigenous peoples and communities to knowledge of psychedelic medicines and healing practices, without which my scholarly contributions would not be possible.

Conflicts of Interest

None to declare

Édition/Editors: Andria Bianchi & Aliya Affdal

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