CHARTING NEW FRONTIERS IN PSYCHEDELIC MEDICINE: A QUALITATIVE EXPLORATION OF PSYCHEDELIC-ASSISTED PSYCHOTHERAPY FOR INDIVIDUALS WITH PSYCHOTIC SYMPTOMS AND CONDITIONS, AND THEIR REPORTS OF PSYCHEDELIC EXPERIENCES

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ABSTRACT

Psychedelics—also known as hallucinogens and entheogens—comprise a family of psychoactive molecules that are both found in nature and synthetically engineered in the lab. As a class, psychedelic compounds produce phenomenologically complex and novel experiences that have recently captured the attention of mental health clinicians and researchers. However, psychedelic clinical research and treatment remain limited, with most studies exploring the efficacy and safety of protocols for individuals with anxiety, depression, substance use, and posttraumatic stress disorder (PTSD), while individuals with personal or familial histories of psychosis, psychotic disorders, and bipolar disorder are mostly excluded from treatment and research.

The overarching objectives of this thesis included determining 1) whether excluding this group from psychedelic clinical research is justified, 2) when psychedelic drug administration and psychedelic-assisted psychotherapy (PAP) may be contraindicated for this group, 3) if people with a history of psychosis or a psychotic disorder may be able to treat their psychotic symptoms with PAP, 4) if people with a history of psychosis or psychotic disorder may be able to treat their co-morbid conditions like anxiety, depression, substance use, or PTSD with PAP, 5) what a PAP treatment protocol for this group could look like 6) how individuals with reported histories of psychosis and psychotic disorders describe their experiences of psychedelic drug use and 7) whether naturalistic psychedelic use has an overall positive or negative effect on emotional well-being and psychological functioning for this group.

Results from the first study—a qualitative study with experts in medicine, mental health, and psychedelics—suggest that certain individuals with histories of psychosis and psychotic disorders may benefit from PAP under the right conditions, such as when psychosis is

etiologically connected to traumatic events, when the protocol offers extensive support for the patient, and when psychosis is not the result of amphetamine use or
medical conditions such as epilepsy. Moreover, results suggest that the effects of the specific psychedelic that is administered must be carefully considered and support outside of therapy must also be assessed. Other factors such as personality traits, ability to form rapport with a guide or sitter, symptom severity, specific symptom endorsement, symptom duration, age, the presence of physiopathology and more must also be taken into consideration.

For the second study, a cross-sectional, retrospective, phenomenological survey report was administered to individuals who reported a history of one or more psychotic experiences and/or diagnosis of a psychotic condition who also had at least one psychedelic drug experience in their lifetime. The survey asked participants to describe one memorable instance of psychedelic drug use and found that in a sample of 100, most individuals (n=88) describe some degree of personal growth resulting from their experience. Many also describe mystical-type experiences, gaining insight or awareness during their experience, heightened appreciation for life, and improved mental health and emotional well-being. Descriptions of symptomatic relief included reduced paranoid thinking, changes in relationships with symptoms, and decreased suicidal ideation. Approximately 11% of the sample described negative experiences including perseverating psychological impairment, symptom exacerbation, and psychedelic-induced suicidality. A slightly larger portion of the sample described mixed-type experiences, i.e., experiencing positive and negative effects alongside each other.

The findings of these studies fill a major gap in the literature by suggesting that individuals with histories of psychotic symptoms and disorders may be able to partake in psychedelic studies and treatment under certain circumstances. This is because experts have

explicitly stated that psychedelic use is not necessarily contraindicated for everyone with psychotic conditions and symptoms, but rather that most PAP protocols for anxiety, depression and other conditions do not offer enough support. At the same time, exclusion criteria are required by the FDA. Additionally, survey reports from individuals with lived experiences of psychosis further back the position that PAP could be a viable treatment option for this group through their survey reports. Specifically, the high prevalence of positive and therapeutic experiences with psychedelics in naturalistic settings suggests that clinically supervised psychedelic drug use may generate similar or even better outcomes for this population. Although a minority had adverse experiences, it remains to be studied as to whether similar effects might be experienced at a similar rate or similar degree of frequency in clinical studies, which utilize harm reduction strategies, maximize safety, and implement preparatory and integration sessions, elements which were notably absent from reports of adverse experiences in the survey. Results also shed light on what a psychedelic treatment protocol could look like for this group, and how individuals with histories of psychotic experiences and diagnosed psychotic conditions describe their experiences of psychedelic use and the effects of psychedelic drugs on their emotional and psychological functioning.

PREFACE

This thesis comprises 6 chapters. Chapter 1 is a General Introduction, Chapter 2 describes the candidate role and contribution to the first study of the dissertation, which was accepted by the International Journal of Mental Health and Addictions Psychedelics Special Issue (by invitation) on June 14, 2023, Chapter 3 is the first study of the thesis, Chapter 4 describes the candidate role and contribution of the second study in the thesis, Chapter 5 is the second the study, and Chapter 6 is a Discussion. Some minor changes in the manuscripts have been implemented to avoid repetitiveness.

Joseph T. La Torre (MTS), the Principal Investigator and Ph.D. candidate in Psychology submitting this thesis, conceptualized all studies, developed hypotheses, designed the studies, interviewed experts in the first study, oversaw data analysis and interpretation of findings, led the creation of the survey in the second study, wrote most of the manuscripts, and prepared manuscripts for submission. Monnica T. Williams (Ph.D.) provided mentorship and support throughout all stages of the studies' execution including methodology and design and contributed to manuscript development. Sonya Faber (Ph.D.) and Kyle Greenway (M.D.) provided mentorship and suggestions regarding neurophysiological and clinical details pertaining to the studies and provided feedback on the manuscripts. Mehdi Mahammadli (B.Sc.) helped with transcribing interviews in the first study, data analysis, survey development, and writing. Jade Gallo (B.Sc.) helped with parts of the second study, namely data analysis, survey development and recruitment, poster development, presenting findings and writing. Daniel Zalewa (B.A.) also helped with the second study by assisting with data analysis, survey development, and writing.

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DEDICATION

I would like to dedicate this thesis to Indigenous and First Nations people around the world who are the traditional knowledge keepers of plant and mushroom medicine.

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ABBREVIATIONS

5-HT1A	5-hydroxy-tryptamine-1A receptor
5-HT2A	5-hydroxy-tryptamine-2A receptor
5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine
APA	American Psychiatric Association
BIPOC	Black, Indigenous and People of Color
BPD	borderline personality disorder
BD	bipolar disorder
CAPE-42	Community Assessment of Psychic Experiences
CBT	cognitive-behavioral therapy
CIA	Central Intelligence Agency
DMT	dimethyltryptamine
Δ-9-THC	Δ-9-tetrahydrocannabinol
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
GAD	generalized anxiety disorder
FEP	first episode psychosis
FGA	first generation antipsychotic
IPA	interpretive phenomenological analysis
KAP	ketamine-assisted psychotherapy
LSD(-25)	lysergic acid diethylamide(-25)
MAPS	Multidisciplinary Association of Psychedelic Studies
MDMA	3,4-Methylenedioxymethamphetamine
MEQ(-30)	Mystical Experiences Questionnaire(-30)

mPFC	medial prefrontal cortex
MDD	major depressive disorder
MRI	magnetic resonance imaging
NMDA	N-methyl-D-aspartate
N,N-DMT	N,N-Dimethyltryptamine
OCD	obsessive-compulsive disorder
OPD	other psychotic disorder
PAP	psychedelic-assisted psychotherapy
PMD	psychotic mood disorder
PPD	psychotic personality disorder
PTSD	posttraumatic stress disorder
PSD	psychotic spectrum disorder
SGA	second generation antipsychotic
SSRI	selective serotonin reuptake inhibitor
TR-MD	treatment-resistant major depression
TR-PTSD	treatment-resistant posttraumatic stress disorder
UPD	unspecified psychotic disorder
WHO	World Health Organization

CHAPTER 1: GENERAL INTRODUCTION

1.1. Overview of Thesis Objectives

The specific aims of this thesis are to determine: 1) whether individuals with psychotic experiences and/or psychotic conditions defined as disorders that feature psychotic-type symptoms and experiences such as psychotic spectrum disorders, psychotic personality disorders, and psychotic mood disorders according to the Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM-5) can safely use psychedelic-assisted psychotherapy (PAP) to treat their psychotic symptoms and/or co-morbid anxiety, depression, substance use, or PTSD, 2) what potential benefits and risks PAP carries for this group, 3) what a protocol for psychedelic treatment could look like for this group, 4) what risk factors for negative treatment outcomes such as symptom exacerbation exist for this group and, 5) how individuals with psychotic experiences and disorders describe their subjective experiences with psychedelics.

These questions were explored in two qualitative studies over the course of three years (2020-2023). The first study utilized an interpretative phenomenological approach (IPA) in which 12 experts in the fields of medicine, mental health, and psychedelic medicine were interviewed to determine why psychedelic clinical trials tend to exclude individuals with psychotic experiences and disorders, if and when this group may benefit from PAP, how one might develop a psychedelic protocol specifically tailored to this group, and what specific psychedelics may be most beneficial for treating psychotic symptoms and disorders. Other questions such as contraindications, psychotic psychopathology etiology, potential benefits, and risks of PAP for this group, and specific needs for this population were also explored. Interview transcripts were coded to identify common themes.

The second study utilized a purposely designed cross-sectional, retrospective online survey that emphasized a qualitative and phenomenological framework and asked individuals with lived experience of psychosis and psychotic psychopathology about their experiences with psychedelic drug use. This participatory approach allowed for data collection regarding reasons for psychedelic use, descriptions of positive, negative, and mixed experiences, and better understandings of experiences of psychedelic drug use for this group, particularly how such experiences affected individuals' emotional and psychological functioning, and descriptions of psychedelic-induced mystical-type experiences. Based on theoretical reasoning and prior literature, relevant variables of interest such as diagnosis, dose, and comfort in setting were also collected (Grof, 1976; Leary et al., 1971). Results were analyzed using inductive thematic analysis.

Findings from the two studies came together to answer the research questions to ultimately determine whether this group could be included in psychedelic clinical research and why or why not. Results also led to understanding precautions and contraindications, and possible considerations surrounding developing PAP protocols for individuals with psychotic experiences and conditions. The first study shed light on potential risks and benefits of PAP for this population, how the field is developing, the role of FDA regulations in study design, and more. The second study highlighted the subjective experiences of psychedelic drug use within this population, bringing forth some of the first data on the topic since the first wave of psychedelic research. Overall, the studies fill a major gap in the literature by answering several key questions that have, up until now, been omitted from the scholarly dialogue or avoided.

1.2. Psychedelics: Classifications and Understandings

The world of consciousness-altering chemicals is rich and diverse; there are thousands of molecules that can induce unique neurophenomenological states. Among some of the most well-known for their potent neurotropic and psychoactive properties are a class of compounds historically grouped under the term 'hallucinogens.' Although a major feature of these compounds is their ability to cause auditory and visual perceptual distortions, they also commonly produce what is known as a mystical experience whereby an individual encounters feelings of euphoria, unity, acceptance, gratitude, love, and transcendence (Barrett & Griffiths, 2018). A pivotal moment in understanding of these drugs in the West was in the 1950s when Humphry Osmond, a British psychiatrist using LSD for the treatment of a range of conditions such as alcoholism and schizophrenia in Canada, proposed replacing the term 'hallucinogen' with the more accurate term 'psychedelic' derived from the Greek roots for 'mind-manifesting' (Tanne, 2004). The nomenclature eventually became mainstream as researchers came to see the drugs' psychological effects as facilitating an unmitigated flow of latent unconscious material to the user. Later, the term 'entheogen' coined by ethnobotanists and mythology scholars in 1979 gained currency within the field for its emphasis on going beyond the material mind and instead focus on the compounds' ability to manifest an internal state of *theos* or an encounter with the Divine (Ruck et al., 1979). Ultimately, however, as a major facet of the psychedelic mystical experience is ineffability, scholars now mostly agree that no one word in any language can fully encapsulate the experiences of these compounds (James, 1982). It is important to acknowledge that a debate has arisen regarding the importance of the acute psychedelic effects in inducing change, with researchers speculating that this class of drugs may be effective without their hallucinogenic components (Cameron et al., 2021; Cooper et al., 2023; Lewis et al., 2023; Moliner et al., 2023).

Numerous psychedelics—naturally occurring, semi-synthetic, and synthetic—exist. Mescaline, found in cacti indigenous to North America is a phenethylamine alkaloid, while lysergic acid diethylamide-25 (LSD-25) also called 'LSD' is obtained from the hydrolysis of alkaloids found in ergot fungus. The potent compound known as dimethyltryptamine (DMT) is known to exist in dozens of plant species and is even produced endogenously by the pineal gland in the human neocortex, while psilocybin is an indole alkaloid produced by over 200 species of *psilocybe* fungi. Classic psychedelics such as the psychoactive tryptamines, phenethylamines, indole hallucinogens, ergotamines, lysergamides, and harmalines are grouped based on the fact that they primarily act on the 5-hydroxytryptamine-2A (5-HT2A) serotonin receptors (López-Giménez & González-Maeso, 2018; Vargas et al., 2023). The psychedelics most well-known to a Western audience are arguably organic psilocybin as found in 'magic mushrooms' and LSD. Other drugs such as MDMA (3-, 4-methylenedioxymethamphetamine), known on the street as 'ecstasy' or 'molly' and ketamine, also called 'K' or 'Special K' are also popular in the West, though they are not classified as classic psychedelics but rather 'non-classic psychedelics.' However, these drugs and other variations, like the classic psychedelics, can also produce mystical and novel experiences of consciousness expansion, which make them important to consider in the context of psychedelic-assisted psychotherapy. For the purpose of this thesis, all of these substances are termed 'psychedelic.'

1.3. A Brief Historical Overview of Psychedelics

It is important to mention that psychedelics are not novel Western innovations or discoveries and that Indigenous and First Nations peoples have used these as medicines for thousands of

years. Indeed, psychedelic plants and fungi have existed on the planet for possibly as long as life itself (Carod-Artal, 2015; Samorini, 2019). Some also believe that humans have used psychedelics for hundreds of thousands of years. One hypothesis known as the stoned ape hypothesis controversially states that our remote prime ape ancestors, once fruitarian and tree-dwelling, ventured down from their canopy abodes and descended upon the plains in search of a more optimal diet (McKenna, 1995). In the process, psilocybin-containing mushrooms, which abound in warm climates, were regularly ingested as a food source. Over the course of tens of thousands of years, psychedelic-induced states of consciousness gradually facilitated species-wide neuroplasticity. Terence McKenna, ethnobotanist and philosopher famously suggested that this may have resulted in rapid brain growth, which in turn led to various forms of creative thinking, language acquisition, art, culture, and philosophical thinking in humans. In other words, McKenna believed that prolonged consumption of psilocybin-containing mushrooms had an evolutionary advantage for humans.

The vibrant *in situ* practices of Indigenous and First Nations persons around the world, particularly in the Amazon Basin, provide us with some of the best anthropological evidence to support the notion that psychedelic plants and fungi had a crucial role in early human culture, namely within the domains of religion, spirituality, and medicine. In 21st-century North America, however, psychedelic healing is not widely perceived as a practice of Indigenous origin, despite having enjoyed being a commonplace human experience in cultures around the world for millennia (McKenna, 1995; Winkelman, 2019). Instead, Western cultural memory influences the more commonly held belief that psychedelics are both dangerous, lack therapeutic effects, and produce experiences that are mere hallucinations with research on psychedelics from the 1940s-1960s (a time called ‘the first wave of psychedelics’) equating

psychedelic-induced states of consciousness to psychosis (Friesen, 2022). This fertile period of research was ended however in 1971 when President Richard Nixon declared drugs a major threat to American society and values. Thereafter, legislation was passed in the United States, Canada, and various countries across the world classifying many psychedelics, such as MDMA and psilocybin, as Schedule 1 drugs in the U.S. and Schedule 3 drugs in Canada—drugs that are highly dangerous with no known therapeutic value.

To this day, MDMA and LSD remain some of the most controlled substances globally, while psilocybin-containing mushrooms maintain decriminalized or legal status a handful of other countries such as Jamaica, Costa Rica, Mexico, and Brazil (Whinkin et al., 2023). During this time of criminalizing psychedelics, the U.S. government, in some cases, even unconstitutionally denied religious and Indigenous groups, such as the First Nations Peyote Church legal use of their sacred plants (Labate & Rodrigues, 2023). It was also during this time that approximately 60 studies on psychedelic medicine's psychiatric effects were shut down (Carhart-Harris & Goodwin, 2017). Today an interest in psychedelics as potentially therapeutic is being restored across North America, South America, Europe, and other parts of the world, however, many researchers still neglect the Indigenous roots of such medicines, problematically seeing the synthesis of psychedelic molecules as novel psychiatric inventions (Tupper et al., 2015).

1.3.1. LSD-25 and *Claviceps purpurea*

Lysergic acid diethylamide-25 (LSD-25), popularly known as 'LSD', was the first psychedelic drug to be synthesized by Western scientists. The story of LSD's so-called discovery and creation is one that is widely romanticized in Europe and North America. Indeed, the day of its

discovery, April 19, 1943, is even widely celebrated as a pseudo-holiday called 'Bicycle Day.' The origins of the story harken back to 1938 when a chemist at Sandoz Laboratories in Switzerland, Dr. Albert Hoffman, was tasked with studying fungus *Claviceps purpurea* or ergot fungus in hopes of finding therapeutic properties (Hofmann, 1983). During the process he synthesized a psychedelic molecule without knowing it. By chance, on April 19, five years after its synthesis, Hofmann accidentally consumed a very high dose of the chemical. Noticing profound distortions in perception and major psychoactivity while at work, Hofmann decided to take the rest of the day off, and have his colleague accompany him back to his house on his bicycle. Thereafter LSD-25, named as such because it was the 25th iteration in Hofmann's synthesis of ergot, quickly became the subject of unmatched curiosity with Sandoz Laboratories manufacturing the drug *en masse* and shipping it to clinicians, therapists, and researchers around the world to research its effects.

LSD is most commonly ingested orally, printed on what are colloquially called 'blotters' or 'tabs', and produces a range of perceptual changes including synesthesia, e.g., feeling colors, euphoria, increased ability to think introspectively, enhanced interoception, and alterations in time perception (Passie et al., 2008). LSD also affects one's ego, or sense of self, and may result in 'ego dissolution.' In high doses, LSD can increase heart rate, blood pressure, muscle tension, and glucose content, which are said to be related to stimulation of the sympathetic nervous system (Olbrich et al, 2021). Ergot infected beverages were likely used for its entheogenic properties connected to LSD as early as ancient Greece (Murasresku, 2020). As LSD is extremely potent, the drug is administered in the microgram range.

1.3.2. Magic Mushrooms

Magic mushrooms, also known as *los niños santos* in Mexico meaning 'the sacred children', and the primary psychoactive compound in them, psilocybin, have been the center of attention in scientific research and cultural interest for many years. Over 200 *Psilocybe* fungi produce this naturally occurring indole alkaloid, and new species are being discovered every year (Matzopoulos et al., 2020; Plazas & Faraone, 2023). Psilocybin acts on 5-HT2A serotonin receptors, and elicits a diverse range of potent psychotropic effects, including distortions in sensing time and space, perceptual distortions, bliss, feelings of unity, and feelings of being spiritually connected to the Universe and all living things (Barrett et al., 2015; Goel & Zilate, 2022). Furthermore, as with LSD, psilocybin and magic mushrooms have been shown to affect one's sense of self and ego, possibly as a result of affecting the default mode network (DMN), a brain network associated with one's ability to self-reference and be introspective (Gattuso et al., 2023). It is important to note, however, that synthetic psilocybin may produce different effects than magic mushrooms since the mushroom contains within it a host of other alkaloids including baeocystin, norbaeocystin, tryptophan, ergosterol, serotonin, and many more that may result in the entourage effect, i.e., pharmacological synergy.

1.3.3. DMT and Analogues

Dimethyltryptamine, commonly known as DMT, and N,N-DMT, is a psychedelic substance that is endogenously produced in the human pineal gland, and when administered exogenously, induces mystical-type experiences in its users (Barker, 2018). It was the first psychedelic drug that received federal approval to be studied after the scheduling of psychedelic drugs during the Nixon era, and was popularized in the book, *DMT: The Spirit Molecule* by the study's principal investigator, Dr. Rick Strassman at the University of New Mexico. N,N-DMT, as with

psilocybin, LSD, and mescaline, also acts through 5-HT2A serotonin receptors, however glutaminergic and neuroprotective sigma-1 receptors appear to also be implicated in its effects (Barker, 2018; Strassman, 2000). The well-known psychedelic concoction known as ayahuasca, which combines the vine of *Banisteriopsis caapi* and the flower *Psychotria viridis* is psychoactive primarily due to the presence of DMT produced by the vine, and the monoamine oxidase (MAO) inhibitor from the flower (Gonçalves et al., 2021). Ayahuasca use is prevalent across Central and South America and is particularly popular in Amazonia. The plant brew is central to the medical and spiritual systems of several Indigenous groups including the Asháninka and Shipibo people. (Luziatelli et al., 2010).

The analog of N,N-DMT known as 5-MeO-DMT (5-methoxy-N,N-dimethyltryptamine) is gaining popularity fast (Weil & Davis, 1993). 5-MeO-DMT, a 5-HT1A and 5-HT2A receptor agonist, targets similar functions in humans, such as changes in auditory and visual perception and self-identity dissolution. However, what is most unique about 5-MeO-DMT is that it is found naturally in the secretion of the glandular fluids of the Sonoran Desert toad, also known as the Colorado River toad or *Bufo Alvarius,* rather than being derived from or found in a plant or fungus. The toad, which lives in the Southwestern United States and Mexico, resides underground for extended periods of time, and only surfaces during the summer months for mating season. Interestingly, while 5-MeO-DMT has been observed to be a profoundly powerful psychedelic experience, it has been described as being free of visual distortions and is significantly more potent than N,N-DMT. Given their ability to generate profound mystical and spiritual states, and impact neuroplasticity, N,N-DMT and 5-MeO-DMT both have considerable therapeutic promise (Reckweg et al., 2020).

1.3.4. Ketamine

The only legal psychedelic substance that is widely used in clinical settings across North America today is ketamine (±)-2-(o-chlorophenyl)-2-(methylamino), although its indicated use is limited to using nasal insufflation of the S enantiomer (esketamine) to treat difficult-to-treat depression. Ketamine was originally classified as an anesthetic and has primarily been used in medical settings for this purpose since 1964. However, it has since also been recognized as a dissociative drug with the ability to produce antidepressant effects and mystical-type experiences (Dore et al., 2019; Hirota & Lambert, 2022). At the beginning of its medical use, some individuals reported unexpected dissociative or out-of-body states which led to its classification changing to dissociative anesthetic. In these instances, individuals who were anesthetized in large doses would sometimes return from their experience and report having had a sensation of travelling somewhere (Treston et al., 2009). These reports were widely circulated in the medical literature and eventually this experience became dubbed ‘the emergence phenomenon’ as at the time, clinicians did not fully understand the drug can produce psychedelic effects.

In the context of ketamine-assisted psychotherapy (KAP), clinicians administer subanesthetic doses to patients (Dore et al., 2019). Two main subanesthetic dose ranges exist: what are known as a ‘trance dose' and a ‘transformational dose’. The smaller trance dose enhances individuals’ ability to engage in therapeutic dialoguing, promotes access to difficult states of mind, and provides transient relief from depressive symptoms and obsessions. The transformational dose on the other hand can reliably generate an out-of-body mystical experience. Ketamine is generally rapid in onset, and its side effects are usually transient and mild and may include headache, and nausea. In cases of abuse, users may experience ketamine-

induced cystitis (Anderson et al., 2022). Ketamine's mechanism of action requires additional research to be fully understood, though it is widely known that while classic psychedelics are primarily serotonergic, ketamine acts on glutaminergic receptors (Zorumski et al., 2016). More specifically, the drug primarily blocks N-methyl-D-aspartate (NMDA) (Halstead et al., 2021). The drug's benefits are also in part attributed to other interconnecting systems, promoting neuroplasticity and synaptogenesis, epigenetics, immunomodulation, and kynurenine pathways (Rybakowski, 2014; Wilkinson et al., 2018).

The most popular route of administration for ketamine is via an intravenous drip bag. Indeed, the United States has seen a dramatic rise in clinics where individuals can pay to receive ketamine intravenously. Ketamine's lipid and water solubility allows it to be administered through this way (Sinner & Graf, 2008). However, it is important to note that this form of ketamine administration is notably different from KAP, which follows the specific protocol of combining psychotherapy with ketamine in three phases, i.e., preparatory, dosing, and integration. Overall ketamine administration and KAP may both provide a promising alternative for individuals with difficult-to-treat conditions as well as persistent and several mental health concerns such as major depressive disorder, obsessive-compulsive disorder (OCD), bipolar disorder, and schizophrenia. However more research must be carried out to understand when ketamine administration and KAP are effective and when these treatments are contraindicated, as well as their differences regarding efficacy, indication, and safety (Block et al., 2012; Gałuszko-Węgielnik et al., 2023; Wilkowska et al., 2020).

1.3.5. MDMA (3,4-methylenedioxymethamphetamine)

As with ketamine, 3,4-methylenedioxymethamphetamine (MDMA) is not classified as a classic psychedelic and is more closely related to amphetamines, though it does produce psychedelic and mystical effects (Dunlap et al., 2018; Kalant, 2001). MDMA is considered an entactogen or empathogen, which fosters interpersonal connection with others, empathy, and derealization (De la Torre et al., 2004). However, it generally does not produce visual distortions although it does facilitate the release of dopamine, norepinephrine, and serotonin. The drug is currently undergoing phase 3 clinical trials for difficult-to-treat posttraumatic stress disorder (PTSD) and has been championed by the Multidisciplinary Association for Psychedelic Studies (MAPS) (Mitchell et al., 2021). MDMA is believed to help facilitate the processing of trauma with the help of a therapist for several reasons. One hypothesized model notes the drug's ability to downregulate amygdala activity and hyperactivate the brain's hippocampal region with the combined effect of permitting users to access deeply stored traumatic memories without fear and discuss them with the supervising clinician (Feduccia & Mithoefer, 2018). While MDMA is itself a synthetic compound, the precursor to MDMA, safrole, is a plant derivative and can be found organically in the tree *Sassafras albidum* (Lunz & Stappen, 2021).

1.3.6. Other Psychedelics

In addition to the above-mentioned psychedelics, there are a host of other uniquely psychedelic plants, mushrooms, and compounds. One such plant is known as *Saliva divinorum*, a member of the sage family that is extremely psychoactive and one of the most potent natural products in the world being active in the microgram range (Coffeen & Pellicer, 2019). It has been used by Indigenous healers for centuries, however, reports of naturalistic use frequently describe the plant as inducing largely dysphoric, terrifying, and disturbing experiences (Zawilska &

Wojcieszak 2013). Peyote (*Lophophora williamsii*) and San Pedro (*Trichocereus pachanoi*), which both contain mescaline, are two cacti that are well known for their ability to induce profound entheogenic experiences (Uthaug et al., 2022). San Pedro is also known as *Wachuma* and is native to the Andes, where it is consumed in the form of a brew (Carod-Artal & Vázquez-Cabrera, 2006). Peyote on the other hand is used by Indigenous groups in the Southern United States and Mexico (Dinis-Oliveira et al., 2019). Other psychedelic mushrooms aside from those mentioned above include *Amanita muscaria*, which has been well documented for its ability to induce highly delirious states of consciousness (Rampolli et al., 2021). Some scholars such as Gordon Wasson have posited that the mushroom was what the Vedic literature called 'Soma', a sacred plant or deity that brought on sacred visions of the Gods and Goddesses (Feeney, 2010). In his book, *The Sacred Mushroom and the Cross,* John Allegro proposes a similar argument that psychedelic mushrooms may have been central to the creation of Christianity (Allegro, 1970). However, there is much speculation that *Amanita* mushrooms could have been a contributing factor to the formation of major religions around the world as the mushroom does not reliably produce entheogenic experiences (de Mattos-Shipley et al., 2016).

1.4. The Reemergence of Psychedelic Clinical Research

Today, psychedelics are reentering the mainstream in the West as potentially therapeutic research chemicals. After a decades-long hiatus and prohibition characterized by anti-drug propaganda and fear, new research is finally being conducted on the possible efficacy of psychedelic medicine in the context of therapy. Over 300 scientific articles on psychedelic-assisted psychotherapy (PAP) in mental healthcare were published in 2022, making PAP a highly discussed topic within the field, and allowing empirically derived information to be accessible to

the public. As a result, the prospective benefits of psychedelics, when used under clinical supervision with a trusted and skilled therapist, are being reconsidered. Some jurisdictions in the United States have even already begun the process of decriminalizing psychedelics like psilocybin-containing mushrooms such as parts of California, Massachusetts, Colorado, and Oregon (Samenow et al., 2023). Some provinces in Canada have made similar adjustments to psychedelic legislation such as Alberta, Ontario, Quebec, and British Columbia (Baig, 2022; Jarvis & Labib, 2022).

MDMA-, psilocybin- and ketamine-assisted psychotherapy have repeatedly demonstrated effectiveness for alleviating symptoms of difficult-to-treat PTSD and difficult-to-treat major depression (Elsouri et al., 2022). In fact, they have been shown to be so therapeutic and safe that the United States government has supported clinical trial research and granted MDMA-assisted psychotherapy a 'breakthrough therapy' in 2012. Since then, several research centers have opened at well-renowned institutions including Harvard University, Yale University, Johns Hopkins University, University of Ottawa, Vancouver Island University, University of Washington, University of California - Berkeley, and the University of Wisconsin - Madison. The Canadian Institutes of Health Research (CIHR) have also started to sponsor psilocybin research in Canada, which is made available to difficult-to-treat patients on a case-by-case basis via the newly enacted Section 56 exemption.

Undoubtedly, the 21st century is witnessing a remarkable shift in thinking regarding psychedelics and their potential role in psychotherapy (Hadar et al., 2023). Previously forbidden for nearly half a century, the exploration into the therapeutic effects of psychedelics is experiencing a resurgence, with the largest-ever conference exploring PAP, Psychedelic Science, having taken place this July 2023 with 12,000 participants in attendance (Rolling Stone, 2023).

As research is opening and studies are uncovering that these drugs possess enormous therapeutic potential while displaying overall favorable safety profiles, clinical societal attitudes are shifting (Kelly et al., 2022). Accompanying a change in perspective are an ease in regulations, a newfound excitement, and cautious optimism, recalling the sudden cessation of psychedelic research that occurred during the 1960s (Kious et al., 2023). Ultimately, a gradual shift in thinking is ushering a new era of clinical research and bringing hope for those suffering from a range of difficult-to-treat conditions.

Although psychedelic research is making progress, one issue that persists is the underrepresentation of marginalized groups in studies, particularly Black, Indigenous, and People of Color (BIPOC) and individuals with stigmatized conditions such as psychotic disorders and bipolar disorder (George et al., 2020; Michaels et al., 2018). While on the surface underrepresentation of BIPOC and exclusion of those with stigmatized conditions may initially appear to be distinct issues, a deeper investigation reveals that the two are interconnected. This is because it is well-documented that Black Americans are burdened by overdiagnosis of psychotic conditions at a disconcerting rate of nearly two times as much as White Americans (Faber et al., 2023). Thus, there exists two groups of individuals diagnosed with psychotic conditions who are being excluded from psychedelic clinical research: those who have inappropriately and inaccurately received such diagnoses—a disproportionate amount of whom are BIPOC—and those who are struggling with genuine psychotic experiences. The potential benefits and risks of PAP for both groups deserve a closer look, as the topic has been conspicuously understudied, and some theoretical reasoning suggests that PAP may be a viable treatment for the latter. When speaking about this issue, it is important to note that several major psychedelic organizations such as MAPS and Johns Hopkins' Center for Psychedelic and Consciousness Studies

systematically bar individuals with psychotic conditions from participating in their research (ClinicalTrials.gov identifier NCT00465595). Exclusion criteria that prohibit anyone with “a first or second-degree relative with schizophrenia spectrum or other psychotic disorders, except substance/medication-induced or due to another medical condition,” and “Bipolar I or II Disorder" are common in the psychedelic clinical research world. That being said, this criterion generally does not exclude individuals with histories of non-pathological forms of psychosis such as drug-induced psychosis or psychotic experiences emerging from sleep deprivation, epilepsy, and other similar conditions.

While inclusion and exclusion criteria are essential for clinical trials, this does not justify the total exclusion of people with histories of psychopathological psychosis or psychotic disorders from psychedelic research, and it remains evident that other factors are directly contributing to this phenomenon. Perhaps the largest factor is the commonly held belief that individuals with familial and/or personal histories of psychotic symptoms and disorders are at a heightened risk of becoming destabilized after psychedelic use—a belief that was introduced during the first wave of psychedelic research, albeit never definitively proven (Dyck, 2005; Friesen, 2023). At the same time, warnings risks of psychedelic-induced psychosis for the general population were continuously touted as part of the curriculum of the War on Drugs.

While inconsistent anecdotal data may suggest that recreational psychedelic use can sometimes catalyze psychotic symptom exacerbation and the manifestation of dormant or latent psychosis in those who are predisposed to developing such a condition, there is no direct evidence to date suggesting that individuals belonging to these groups cannot safely partake in supervised psychedelic therapy (La Torre et al., in press). Indeed, it is also important to note that incidents where naturalistic consumption of psychedelics have resulted in adverse and negative

consequences for this group are almost exclusively associated with use in improper setting, such as being unsupervised, being given too strong a dose, or even being forcefully administered the drug(s) in the context of human experimentation (Rucker et al., 2017). Another factor that may be contributing to the surge of interest in studying PAP for individuals with anxiety, depression, PTSD, and substance use disorder is that these populations are assumed to be associated with less risk, despite a lack of modern studies empirically demonstrating this (Johansen & Krebs, 2015). Comparatively, bias, fear, and stigma with deeply embedded historical roots likely contribute to the lack of psychedelic research for people with psychotic conditions such as bipolar disorder and schizophrenia.

1.5. Psychotic Symptoms as Psychedelic Exclusion Criteria

With the growing shift from a purely biological approach to integrated approaches to treating psychotic conditions that include psychotherapy, supported by an abundance of empirical studies demonstrating the effectiveness of psychotherapy for psychotic symptoms, it is time to reconsider when and how excluded patients with psychopathological experiences of psychosis, psychotic spectrum disorders, and other similar mental health diagnoses that feature psychotic experiences may benefit from psychotherapy coupled with psychedelic dosing (Arnovitz et al., 2022; Mahmood et al., 2022; Turner et al., 2014; Wolf et al., 2022; Zeifman & Wagner, 2020). In addition, it is time for the field to consider how systematic exclusion of individuals with said conditions and experiences may be impacting people of color, particularly BIPOC communities, who are regularly overdiagnosed with these highly stigmatized conditions (Faber et al., 2023; George et al., 2020; Michaels et al., 2018).

The studies in this thesis draw on the clinical and theoretical knowledge of psychedelic researchers and practitioners to understand why certain individuals with psychopathological experiences of psychosis and psychotic disorders such as those mentioned above are excluded from PAP, the implications of this exclusion, the possibility of including this group in psychedelic research, why PAP may be a viable treatment option for those with psychosis and/or psychotic diagnoses, and how individuals with these experiences and disorders report and describe their psychedelic experiences. Namely, the studies seek to explore if the exclusion criteria as outlined in psychedelic clinical trials of having a personal or familial history of a psychotic disorder or psychotic symptoms of psychopathological origin may be valid, and why or why not (ClinicalTrials.gov identifier NCT00465595).

1.6. Definitions of Psychosis and Psychotic Symptoms

Psychosis has many definitions as it exists on a spectrum, ranging from brief experiences of atypical perceptions to chronic and pervasive psychosis. In modern clinical practice, reflected in both the respective classifications of the World Health Organization (WHO) and the American Psychiatric Association (APA), psychosis refers to a range of symptomatic experiences. These may be separated into two primary symptom domains: 'positive symptoms' referring to the presence of symptoms such as hallucinations, delusions, disorganized speech/thought, and disorganized motor, and 'negative symptoms,' which refer to deficits such anhedonia, avolition, and blunted affect. These symptoms vary markedly in presentations, severity, and evolution (Arciniegas, 2015). According to the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), mental health conditions that feature psychotic symptoms occur on a continuum, are often chronic or prolonged, and primarily include psychotic spectrum disorders such as first

episode psychosis and schizophrenia, mood disorders such as bipolar disorder I and II and major depressive disorder with psychotic features, personality disorders such as borderline personality disorder (BPD), schizoid, and schizotypal personality disorders, and can also occur in PTSD (American Psychiatric Association, 2013; Burton et al., 2018; Dubovsky et al., 2021; Murrie et al., 2020). This list is not exhaustive, and many other conditions may feature psychotic experiences including but not limited to dissociative identity disorder and other dissociative disorders.

It is also important to note that someone can have psychotic symptoms or experiences without having one of the aforementioned mental health disorders. For example, someone can experience hallucinations or delusions, however, these experiences alone do not warrant a diagnosis. Furthermore, experiences of psychosis have also been observed in individuals as a result of non-psychological conditions such as epilepsy, and may occur due to various etiologies including genetic, environmental, and mixed factors (Arciniegas, 2015; Nadkarni et al., 2007). Drugs such as methamphetamine and even environmental factors such as sleep deprivation are also both associated with psychosis symptoms onset (Ham et al., 2017; Waters et al., 2018). It is worth mentioning that experiences of what is called 'spiritual emergence'— interchangeably called ‘spiritual emergency’— may also resemble psychosis, however, is a distinct phenomenon that requires different treatment procedures (Kaselionyte & Gumley, 2019; Sharma et al., 2009). As Christina and Stan Grof describe, “[...] many of the conditions, which are currently diagnosed as psychotic and indiscriminately treated by suppressive medication, are actually difficult stages of a radical personality transformation and of spiritual opening. If they are correctly understood and supported, these psychospiritual crises can result in emotional and psychosomatic healing, remarkable psychological transformation, and consciousness evolution (Grof & Grof, 1989).”

1.7. Psychosis and Culture

Experiences that would be labeled as psychotic in Western psychiatry are readily observed in Indigenous and First Nations communities around the world where they are sometimes understood differently. In some cultural contexts, especially in those where shamanism is practiced, it is not uncommon for individuals with experiences like voice-hearing or seeing deceased ancestors to be viewed as possessing unique spiritual abilities that permit them access to different channels the average person cannot rather than being seen as mentally ill as in the West (Fotiou, 2019; Powers & Corlett, 2018). Moreover, within some Indigenous communities, such as those in the Amazon Basin, Tibet, or in Siberia, individuals with these experiences may not be stigmatized or pathologized and instead, may partake in psychedelic plant ceremonies, without any evidence of a worsening of their mental status (Dos Santos et al., 2017; Taussig, 1987).

Although this does not prove psychedelics are safe for all people with psychosis or psychotic conditions, it does lend evidence to the idea that some people with psychotic experiences may benefit, or at least not be harmed, using psychedelic substances. At the same time, it is important to note that traditional societies may still have cultural conceptualizations where people with psychotic experiences are understood as sick, particularly when symptoms rise to the level of functional impairment (Cohen et al., 2016). All this to say, a full accounting of psychedelics and psychosis necessitates not just an examination of first wave psychedelic research, but also living traditions and their thousands-years old histories and practices.

1.8. Models of Psychosis and Psychotic Conditions

A range of etiological models and schools of thought shape our understanding of psychosis pathogenesis, psychotic psychopathology perpetuation, and treatment approaches spanning an emphasis on biogenetic vulnerability, cognitive processes, behavior, and psychosocial factors. Current understandings consider psychosis and psychotic disorders, like other mental health conditions, brought forth due to psychological factors, environment, social interactions, genetic and predisposition (Al-Diwani et al., 2017). Thus, psychotic disorders are believed to be polygenic, caused by complex interactions between a myriad of factors. These converge in a wide variety of higher-level effects on neural oscillations and circuitry, which are in turn reflected in changes in cellular machinery down to the level of ion channels, and transcription changes with over 100 genetic sites have been identified as contributory (Endres et al., 2019; Mäki-Marttunen et al., 2019; Misiak et al., 2021; Sekar et al., 2016; Zwicker et al., 2018). Beyond genetics, substance use, pathogens, and psychological trauma may also result in alterations to synaptic connectivity. Developmental processes can likewise result in abnormal synaptic connectivity, e.g., excessive synaptic pruning has been implicated in the development of schizophrenia (Germann et al., 2021).

Potential biological contributing factors of psychosis have been observed in several contexts. For example, people with schizophrenia show minor decreases in brain tissue volumes during first episode psychosis (FEP) as seen in multiple MRI studies (Murray & Lewis, 1987). Furthermore, early research demonstrates higher incidence rates of schizophrenia in those who have familial histories of those with the disorder compared to the general population (Heston, 1966). However, such fundings are outdated and the volume decreases may be readily attributed to the effects of antipsychotics and substance use. Additionally, it is now known that schizophrenia's genetic architecture is significantly more complex than previously thought

(Gejman et al., 2011). It is also important to note that the investigation into schizophrenia and psychotic disorder pathogenesis relies primarily on correlational research, limiting the robustness of etiological research.

Some research defines psychosis as a progressive brain disease, positing that a loss of gray matter may be treated with purely pharmaceutical treatment approaches, despite neural and genetic findings being largely nonspecific, inconsistent, and of small magnitudes in the case of positive symptoms (Scheepers et al., 2018; van Haren et al., 2008). The notion that forms of psychosis such as schizophrenia are progressive brain diseases has also been challenged (Zipursky, 2013). Likewise, there is debate as to whether there is concrete evidence demonstrating the neurotoxicity of psychosis on the nervous tissue of the brain when there is a lack of active intake of antipsychotics (Moncrieff & Leo, 2010; Navari & Dazzan, 2009). Indeed, in a critical review of 35 studies exploring the psychosis-neurotoxicity hypothesis, 21 of them did not support the hypothesis, rendering the validity of the hypothesis questionable at best (Rund, 2014). However, there appears to be solid evidence demonstrating that positive psychotic symptoms are related to increased dopamine in the mesolimbic pathway, while negative symptoms are related to decreased dopamine in the mesocortical pathway (Stahl, 2000).

At the same time, any review of etiological models of psychosis and schizophrenia would be remiss to exclude the dopamine hypothesis formulated by van Rossum in 1966, which posits that hyperactivation of dopamine receptors in the brain are responsible for experiences of psychosis (van Rossum, 1966). This hypothesis was inferred based on the observations that may antipsychotic medications suppressed dopaminergic activity in the brain. However, since its inception, has been criticized for being overly simplistic (Howes et al., 2019; Millard et al., 2022; Moncrieff, 2009).

While psychotic disorders do not appear to be exclusively the result of biogenetic predisposition or biophysiological processes such as cortical degeneration or dopamine hyperactivation, literature strongly suggests that genetic vulnerability and dopamine do play a role in the development of psychotic processes (Millard et al., 2022; Stilo & Murray, 2019; Wahbeh & Avramopolous, 2021). However, much of the evidence supporting the significance of these physiological processes are based on correlational observations, limiting their overall reliability. Other factors that are believed to contribute to the onset of these illnesses, possibly by effecting physiology or neurotransmitter activity in part, include psychosocial factors such as trauma, pregnancy and birth complications, migration, social isolation, and living in urban environments. Other possible contributing factors to the alteration of cortical brain volumes in patients with schizophrenia factors include smoking, cannabis use, alcohol use, and other environmental stressors.

In it important to note that an emphasis on putative neurological abnormalities as causes of psychosis such as the dopamine hypothesis, and brain-based explanations of psychedelic effects such as the entropic brain and serotonin hypotheses are reflective of psychiatry's turn to the brain, which occurred during the 20th century and prioritizes biogenetic etiological understandings of psychological experiences (Frounfelker, 2010). In contrast, increasing evidence demonstrating that psychosis is a product of both environmental and biological genetic causes has generated renewed interest in the role of environmental influences on psychosis, particularly trauma (Bendall et al., 2013). In particular, it is important to acknowledge that a wealth of literature supports the existence of a subset of individuals who experience trauma as a causal factor of their psychotic symptoms as suggested by studies outlining a robust correlational relationship between childhood trauma, particularly sexual abuse, and psychotic disorders

(Bechdolf et al., 2010; Bendall et al., 2008; Read et al., 2005; Thompson et al., 2014). Individuals who have experienced at least one traumatic event are more likely to exhibit psychotic symptoms and have a 20% increased risk of persistent mental/emotional stressors relative to the general population (Benjet et al., 2016; Buckley et al., 2009; Kilcommons & Morrison, 2005). Likewise, this population is approximately three times more likely to have experienced childhood adversity than controls. At the same time, it is important to note that these observations, like many of these made to back neurophysiological explanations of psychosis, are also limited by being correlational in nature.

Despite the growing evidence for environmentally facilitated psychotic symptoms, one reason why a narrow genetic-origins model may be more commonly accepted within psychiatry is that current psychodiagnostic nosology blurs the line between the model of trauma-induced psychotic disorders and PTSD (Morrison et al, 2003). For example, it is possible that the DSM-5 criterion of the presence of "marked stressors" for brief psychotic disorder mischaracterizes the potential for delayed onset (prolonged gestation) of the effects of trauma in people presenting with psychotic symptoms. Cases of trauma being the primary precipitant for the development of hallucinations, dissociation, delusional thinking, and similarly debilitating symptoms generally lead to a diagnosis of PTSD, raising questions about the meaningfulness and utility of drawing clear distinctions between psychotic disorders and PTSD. Furthermore, the highly filtered recognition of traumatic events according to the DSM-5 that, as an example, excludes experiences of racism and discrimination, undermines the far-reaching complexity and variety of trauma (Holmes et al., 2016; Stowkowy et al., 2016; Varchmin et al., 2021). However, it is worth noting this is a nonissue when the International Classification of Diseases 11th Revision (ICD-11)

is used due to its focus on symptom manifestation rather than specific preceding events (World Health Organization, 2022).

Meanwhile, according to the cognitive-behavioral therapy (CBT) model, which was established by Aaron Beck in the 1960s and has since shown to be efficacious in treating a range of problems, psychosis and schizophrenia is ultimately a cognitive and behavioral issue (Chand et al., 2023; Kahn et al., 2015). Specifically, it is believed that psychotic disorders are an information processing issue. As such, CBT and other similar psychotherapeutic approaches to treating psychotic conditions involves focusing on the individual's beliefs regarding their psychotic experiences, understanding their specific coping strategies within the context of their psychotic symptoms, and seeking to correct and challenge their thoughts such as catastrophic appraisals based on objective evidence with the goal of modifying behavior and emotional wellbeing (Batinic, 2019; Sommer at el., 2012). As the cognitive-behavioral model emphasizes an etiological focus on the bio-psycho-social model, CBT is usually used to in tandem with pharmacological treatments rather than in isolation.

Ultimately, integrative models that consider myriad causal factors encompassing genetic vulnerability, psychological and developmental processes, cognitive factors, and epigenetic and psychosocial determinants are most effective for understanding the etiological processes underlying psychotic symptomatology, as well as for navigating treatment options. It is also worth mentioning that integrative models of psychotic disorder pathogenesis have clear implications for PAP, specifically for considering which psychedelic compounds may be effective tools for helping to modify high-level beliefs for this population, process trauma where it exists, and treating co-morbid conditions like anxiety and depression (Carhart-Harris, 2019; Feduccia & Mithoefer, 2018).

1.9. Exploring Key Psychedelic Paradigms

There are multiple paradigms and theoretical frameworks that offer insight into how psychedelics may affect the brain and the mind, and how PAP drives behavioral and psychological changes. These include models that are primarily rooted in physiology such as the default mode network (DMN) hypothesis, and serotonin hypothesis, and those that are predominantly focused on psychological processes such as the psychodynamic approach and psychotomimetic model. Additionally, there are paradigms which lay somewhere in between the two such as the entropic brain hypothesis, and self-entropic broadening (SEB) hypothesis. There also exists a school of thought that emphasizes the significance of mystical experiences in producing therapeutic outcomes. All are interrelated in meaningful ways, and share some overlap, though each offers a distinct primary proposition. Each can also help shed light on whether individuals with histories of psychotic symptoms and psychotic conditions can safely use PAP to treat their psychosis and/or other co-morbid disorders, and why or why not.

The serotonin hypothesis stands out as a prominent working model in psychedelic clinical science and highlights the role in which serotonin receptors, and more specifically the 5HT2A receptor, play in the mediation of psychedelic experiences (Madsen et al., 2019; Girn et al., 2022). Serotonin and its respective receptors have been noted to be associated with mood, body temperature regulation, stress response, appetite, and sleep (Jones et al., 2020; Kanova & Kahout, 2021). Serotonin 5HT2A receptors have notably been identified as playing a key role in learning, a range of cognitive functions, sensory perception, and goal-directed behavior (Aznar et al., 2016; Zhang & Stackman, 2015). It is interesting to note that psychedelics such as LSD and psilocin (the metabolite of psilocybin) have demonstrated remarkable binding affinity to

serotonin receptors, even surpassing serotonin itself (López-Giménez & González-Maeso, 2018; Rickli et al., 2016). This hypothesis thus posits that the disruption of serotonin signaling and subsequent binding of psychedelic molecules to serotonin receptors may be the primary mechanism by which psychedelics facilitate mood improvement and behavioral, as briefly described above.

An offshoot of the serotonin hypothesis goes further to speculate that not only does serotonin play a role in psychedelic experiences, but that the alterations in neurotransmitter activity induced by psychedelics may be all that is needed. Indeed within the last few years, research is exploring if the experiential component of psychedelics—their acute effects such as visual imagery, mystical-type experiences, and perceptual and sensorial distortions—may be superfluous and unnecessary for eliciting therapeutic outcomes (Cameron et al., 2021; Lewis et al., 2023). Similar hypotheses have been advanced about the role of tropomyosin receptor kinase B (TrkB) receptors, which interact with serotonin 5HT2A receptors (Ilchibaeva et al., 2022; Moliner et al., 2023). These theoretical frameworks suggest that non-hallucinogenic analogues of psychedelics like LSD and psilocybin may produce similar behavioral changes to their hallucinogenic counterparts without the psychedelic components. Not without controversy, this area may hold promise for treating individuals with psychosis and other conditions who may exhibit unfavorable responses to hallucinogenic psychedelics. Nevertheless, more research must be carried out to better understand if the serotonergic effects of psychedelics are separable from their perceptual and sensory effects, and if so, to what extent.

Another important theoretical model, which highlights the role of physiology in psychedelic experiences portrays the default mode network or ‘DMN’ as playing a central role in the behavioral and psychological changes commonly seen in PAP. The DMN is a novel network

in the brain that includes the medial prefrontal cortex, precuneus, and posterior cingulate cortex (Buckner et al., 2008). Together, this network enables functional tasks such as self-awareness, mental time travel, autobiographical thinking, and other abilities (Fingelkurts et al., 2012; Otsby et al., 2012). Thus, it is interesting and important to note that psychedelics cause a marked decrease in activity and connectivity in the DMN and increases in interconnectivity and excitability in the posterior association cortex, and the medial temporal lobe (Palhano-Fontes et al., 2015; Riba et al., 2004; Riba et al., 2006). A similar and related hypothesis specifies that in addition to the decrease in activity of the DMN, which results in de-identification with the self, the observed downregulation of amygdala activity and hyperactivation of the hippocampus may help to facilitate the processing of traumatic memories with a therapist (Feduccia & Mithoefer, 2018). By downregulating the brain's fear response and increasing one's ability to access deeply stored memories, individuals become more capable of retrieving and discussing memories of traumas and adverse life events in the presence of a clinician. As such, the effects of psychedelics on the DMN may be relevant to understanding how PAP may benefit individuals with psychotic conditions, particularly those who would like to process traumatic memories in therapy. The transient deactivation of the DMN during psychedelic dosing, which has been likened to a neuropsychological 'reset' may also harbor the potential to treat people in psychotic states (Gattuso et al., 2023; La Torre et al., in press).

A separate line of reasoning that runs counter to understandings that prioritize biophysiological processes is based on an older corpus of literature and theory that prioritizes a Freudian system of psychology, behavior, and consciousness, popularized during the first wave of psychedelics (circa 1950s-1960s) (Carhart-Harris & Friston, 2019). This school of thought holds that psychedelics, as the etymological meaning of the word suggests (see page 2) help to

relax one's ego defense mechanisms in a manner that permits unconscious material to become realized on a conscious level. Stan Grof, a prominent psychedelic-psychodynamic theoretician-practitioner at the time proposed that in this sense, psychedelics may be understood as "non-specific amplifiers," causing belief systems, memories, and other related psychological processes that may be repressed to not only become accessible and known, but also more pronounced and intensified (Grof, 1976). As such, this model can be integrated with neurophysiological processes that could make changes in consciousness possible. However, within this framework, attention to biological processes is traditionally and typically secondary to the primary principle of unconscious material becoming experienced consciously as it were. As such, the psychodynamic model suggests that individuals with a range of conditions, including psychosis, may benefit from supervised psychedelic use to access repressed unconscious material such as repressed traumatic memories that may be directly affecting them and contributing etiologically to psychopathology.

Another paradigm that emerged during the first wave of psychedelic research is the psychotomimetic or psychomimetic model (Nichols & Walter, 2021). This framework understands states of psychosis and psychedelic experiences as one in the same, equating the two and emphasizing the similarities between them such as the presence of perceptual distortions and altered sensory experiences. While the two do display similarities, it is important to note that they are also markedly different, and that this model is overly simplistic in nature (Dourron et al., 2022; Rajpal et al., 2022). Although psychedelics can produce states that may superficially resemble psychosis, they are characteristically and phenomenologically different, with the former being transient and occurring only when the drug is in the system perceptual effects diminishing after metabolization of the drug. On the other hand, the latter is a chronic,

psychopathological phenomenon that is brought on by a range of biological and epigenetic factors over a long period of time. While some believe the psychotomimetic model is useful, it has been a topic of serious debate and its utility as a theoretical foundation of psychedelic research is questionable, carrying with it considerable risk of perpetuating stigma both for individuals with psychotic conditions and for psychedelics.

Two hypotheses that stand between the biophysiological models centering serotonin and the psychodynamic approach to psychedelic-induced states of consciousness are the entropic brain hypothesis and the self-entropic brain hypothesis (SEB). The entropic brain hypothesis is a theoretical framework posited by Carhart-Harris and colleagues (2014) and is one of the most popularly cited and accepted theoretical frameworks in the field of psychedelic science. It posits that brain activity, cognition, and behavior exist on a continuum, with one end characterizing mental states that are notably rigid and the other, those that are in a state of high entropy or chaos, with psychedelic states of consciousness being highly entropy states due to their characteristically interconnected and free-flowing-like state. Interestingly, according to this model, individuals with psychotic symptoms are thought to also be in a highly entropic state, which some clinicians see as grounds for thinking that psychedelics as likely to potentiate and exacerbate psychosis for those with symptoms or a disposition regardless of set and setting. Contrary to the entropic brain theory, it is possible that psychotic symptoms could be interpreted as a highly fixed state of mind, as people with psychotic symptoms may also be seen as endorsing rigid sets of behaviors and beliefs given that DSM-5 defines delusions as “fixed beliefs that are not amenable to change in light of conflicting evidence” (American Psychiatric Association, 2013). As such, there may be fundamentally sound reasons to include, rather than

exclude, persons with psychotic symptoms such as psychedelics' ability to increase psychological flexibility based on the entropic brain theory (Close et al., 2020).

A related theory, which builds off the entropic brain theory is called the self-entropic broadening (SEB) theory proposed by Dourron et al. (2022), which suggests that psychedelics may be beneficial to those with psychosis. The SEB theory points out that while psychotic and psychedelic states have notable similarities, they also have significant differences. Specifically, this theory states that while both can feature high levels of creativity, heightened attentional awareness, and decreased predictability in cognitive processing, they differ in terms of self-perception. Individuals with psychosis tend to be hyperfocused on themselves, frequently interpreting events, or actions in relation to their experiences, perpetuating delusional thinking. The SEB theory suggests that on the other hand, psychedelics can allow people to shift away from being self-focused and instead increasing focus on the world around them, and thus could potentially be therapeutic to people with psychotic symptoms.

Another influential perspective that has contributed significantly to the field of psychedelic clinical research, particularly in the United States, is the school of thought that sees PAP outcomes as closely tied to mystical-type experiences they can induce. This theoretical framework has led to a reinterpretation of the effects of psychedelics as 'entheogenic,' speaking to the drugs' capacity to induce internal religious or spiritual experiences. Notably, pioneering researcher Dr. Roland Griffiths has played a crucial role in this line of reexamination with his research on how psilocybin-induced mystical experiences can catalyze dose-related behavioral changes in individuals suffering from a range of conditions including depression, end-of-life anxiety, and tobacco addiction (Barrett & Griffiths, 2018; Garcia-Romeu & Griffiths, 2014; Griffiths et al., 2006; Griffiths et al., 2008; Griffiths et al., 2011; Griffiths et al., 2016). Others

who have followed this trend have also uncovered similar findings with psilocybin-induced mystical experiences and increases trait openness (MacLean et al., 2011). Additional similar avenues of research have found that numinous experiences such as 'entity encounters' are a common experience with psychedelic substances such as DMT (Davis et al., 2020). As a result of this growing body of research, it is common to include variations of the Mystical Experiences Quesionnaire-30 (MEQ-30; Pahnke, 1963) in psychedelic clinical research. The inclusion of this measure is multifold, and usually serves the purpose of better understanding if scores are correlated to PAP treatment outcomes and types of experiences individuals can have.

All this to say, a range of intersecting paradigmatic frameworks exist for understanding and explaining and studying the mechanisms by which psychedelics exert their behavioral and psychological effects. These models can be characterized as existing on a spectrum, which sees biological processes existing on one end and psychological processes existing on another, with some sitting in between the two. All contribute in meaningful ways to the dialogue surrounding how psychedelics may help individuals suffering from a range of conditions and the potential role they can play in augmenting psychotherapy. Each emphasizes different elements and sheds light on how psychedelics could affect individuals with psychosis and psychotic conditions, as well as whether PAP could be of benefit to this group, and specifically how.

1.10. Current Treatments for Psychotic Symptoms

As we consider PAP for people with psychopathological psychosis and psychotic disorders, it is important to acknowledge that several treatment options exist for this group. These include pharmacological interventions, the administration of antipsychotics in tandem with psychotherapy, electroconvulsive shock therapy (ECT), and transcranial magnetic stimulation

(TMS) (Ali et al., 2019; di Hou et al., 2021; Focht & Kellner, 2012; Lévy-Rueff, 2008; Stultz et al., 2020). Commonly administered medications include first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs), and frequently utilized psychotherapies include cognitive-behavioral therapy (CBT), positive psychotherapy for psychosis (PPP), acceptance and commitment therapy (ACT), and similar psychotherapeutic modalities (Chadwick, 2014; Choi et al., 2023; Chu et al., 2022; Johns et al., 2016; Kasperek-Zimowska et al., 2020). Each approach offers benefits; however also comes with its own set of limitations, risks, and challenges.

First-generation antipsychotics (FGAs) or 'conventional antipsychotics' which were discovered in the 1950s differ from second-generation antipsychotics (SGAs)—also known as 'atypical antipsychotics' or 'atypical neuroleptics'—in significant ways, particularly regarding their binding affinity to neurotransmitter receptors and receptor activity (Lopez-Gil et al., 2010). The discovery of SGAs in 1980s marked the last major milestone in the pharmacological treatment of psychotic disorders (Shen, 1999). While the invention of SGAs was seen as a breakthrough at the time and led to deinstitutionalization, evidence accumulated in the intervening years has resulted in a re-evaluation of treatment models focused solely or primarily on antipsychotic medications. While response to antipsychotic medications are heterogenous and inconsistent, what remains consistent is prevalence of side effects that occur in individuals, including but not limited to weight gain, cardiometabolic dysfunction, cholesterols increase, and symptom exacerbation (Ascher-Svanum et al., 2010; Rummel-Kluge, 2010).

At the same time, it is interesting to note that efficacy rates of antipsychotics are cited as the top reasons for both medication continuation and discontinuation with up to one third of patients being non-responsive to antipsychotics (Nucifora et al., 2017). It is also important to note that evidence demonstrating the superiority of SGAs efficacy rates to FGAs is lacking

(Meyer, 2007). The U.S. Food and Drug Administration (FDA) has approved 11 different FGAs with the most prescribed being chlorpromazine, perphenazine, and haloperidol, with recent epidemiological data indicating that approximately 2 million adults in the U.S. taking SGAs such as clozapine, risperidone, and quetiapine (Abou-Setta et al., 2012; Wang et al., 2009).

Current perspectives now recognize that psychotherapy is essential in the treatment of primary psychotic disorders, in combination with medications (McDonagh, 2021). Cognitive-behavioral therapy (CBT) with its focus on symptom management has demonstrated improvements in tackling delusions and hallucinations while mitigating the side effects of traditional antipsychotic drug treatment (Sitko et al., 2020). CBT for psychosis (CBTp) is often used in conjunction with pharmacological interventions due to evidence suggesting that a combinatory approach is synergistic and interactional (Moritz et al., 2019). As such, a range of other psychotherapeutic modalities are employed in a similar method including positive psychotherapy for psychosis (PPP), acceptance and commitment therapy (ACT), and metacognitive and mindfulness approaches (Chadwick, 2014; Choi et al., 2023; Chu et al., 2022; Johns et al., 2016; Kasperek-Zimowska et al., 2020). Combinatory modalities are motivated by the fact that many people with diagnosed psychotic conditions express interest in forms of care other than those focused administering solely pharmacological interventions due to unsatisfactory results and a range of detrimental and negative side-effects (Oh et al., 2020; Whale et al., 2016).

Other treatment approaches include electroconvulsive shock therapy (ECT) as well as transcranial magnetic stimulation (TMS). Research demonstrates that ECT can be an effective approach for treating those with psychotic symptoms and disorders, particularly those with difficult-to-treat schizophrenia and postpartum psychotic depression, however risks must be

considered such as the possibility of cognitive impairment (Ainsworth et al., 2022; Ali et al., 2019; Focht & Kellner, 2012; Lévy-Rueff, 2008; van Diermen et al., 2018). Meanwhile transcranial magnetic stimulation or TMS has also demonstrated to be one potential avenue for treating psychotic symptoms and preventing the progression of disorders like schizophrenia, while maintaining a favorable safety profile, with one literature review determining the risk of TMS-related seizures to be <1% (Baliga & Mehta, 2021; di Hou et al., 2021; Stultz et al., 2020). However, although TMS has been shown to treat both negative and positive symptoms of psychosis, it is important to note that results are inconsistent and effect sizes are small (Mehta et al., 2019).

Several treatment options exist for individuals suffering from a range of psychotic symptoms and disorders including depression with psychotic features and schizophrenia. These include but are not limited to antipsychotic medications, pharmacologically assisted psychotherapy, electroconvulsive shock therapy (ECT), and transcranial magnetic stimulation (TMS). As treatments are limited, carry risks, can produce a range of side-effects, and offer poor efficacy rates overall, exploring experimental avenues such as psychedelic-assisted psychotherapy is important to address the unmet needs of this population.

1.11. The First Wave of Psychedelic Research

Much as was the case for diverse psychiatric diagnoses, harms for patients with psychotic disorders have been reported in studies of the first wave of psychedelic research, in addition to benefits. After the occurrence of the first wave of psychedelic research, which began in the 1950s and subjected hundreds if not thousands of persons with severe and persistent mental health conditions to inhumane experimentation with psychedelic substances, persons with

psychopathological experiences of psychosis stopped being included in psychedelic research (Nichols & Walter, 2021; Strauss et al., 2021). Reasons for this exclusion vary. Lack of strong social support systems, which is often a reality for individuals with marginalized and stigmatized mental illnesses such as psychotic spectrum disorders, bipolar disorder, and similar conditions is one possible reason to exclude this population from psychedelic research. Likewise, the lack of research examining the physiological effects of greater sensitivity to dopaminergic drugs in patients with psychotic disorders may also be one reason to exclude this group as more safety research must be done to determine how psychedelics affect dopamine (Kesby et al., 2018; Vollenweider, 2001). On the other hand, misperceptions forged during early psychedelic research along with the political and legal machinations that followed may also underlie such exclusions.

Prior to and during the first wave of research, psychedelics were often seen as psychotomimetic, i.e., mimicking psychosis, and this idea was widely disseminated in scientific literature and later brought into the public sphere by popular media and political campaigns (Swanson, 2018). Such a link was supported by studies demonstrating that psychedelic substances elicit experiences that resemble those found in chronic psychotic disorders. However, findings from the first wave of psychedelic research, which included individuals with schizophrenia and similar conditions report inconsistent findings and were often conducted under poor conditions, lacked methodologically sound protocols, involved misdiagnosis, and adhered to unregulated dosing as well extremely high doses (Strauss et al., 2021; Swanson, 2018).

It is also worth noting that one possibility for why individuals with psychopathological experiences of psychosis, psychotic spectrum disorders, bipolar disorder and related conditions are currently being excluded from psychedelic clinical trials is because regulatory agencies such

as the U.S. Food and Drug Administration (FDA) require new medications and treatments to include both indicated and contraindicated conditions. In addition, there may also be pressure to study psychedelic therapy for individuals with less stigmatized conditions such as psychotic spectrum disorders, bipolar, and borderline personality disorder to ensure the utmost safety of patients. Exclusion may also be followed at present due to presumptions regarding adverse reactions in individuals with said conditions because of biases formed during the campaign against drugs during the Nixon era, which popularized the idea that psychedelics are dangerous and that psychedelic-induced psychosis is a risk for everyone (Hall, 2022; Siff, 2015).

It is not uncommon to treat, assess, or hear of cases where individuals with a history of psychosis or a predisposition to developing psychotic symptoms become destabilized after using psychedelics recreationally (La Torre et al., in press). However, generalizing this observation to psychedelic-assisted therapy without empirical research is premature. It is important to acknowledge the numerous layers of barriers have impeded empirical research from being carried out on the effects of psychedelics on people with psychosis and psychotic conditions, and discussions on the therapeutic applications of psychedelics for these conditions are often dismissed or ridiculed. Indeed, it is worth noting that the first study in this dissertation was subjected to unfair criticism when submitted to peer-reviewed journals on more than one account with reviewers openly expressing their biases and fears, though the first manuscript was later accepted by a high impact peer-reviewed journal.

1.12. Considerations and Possible Contraindications

There are several considerations that must be addressed when determining if PAP may be a viable treatment option for those with psychosis or psychotic conditions, and a discussion of

possible contraindications is imperative. One important consideration involves determining what kind of psychedelic substance may be most appropriately administered for members of this group, and which risks each carry. For example, the literature clearly demonstrates that some substances, particularly cannabis-derived Δ-9-tetrahydrocannabinol (Δ-9-THC) and amphetamines, may exacerbate, accelerate the onset of, or even lead to the development of psychotic symptoms in some individuals (Hasan et al., 2020; Henning et al., 2019). Given that MDMA is an amphetamine, it would be important to consider these risks, particularly in the context of the dopamine hypothesis, which warrants caution surrounding the use of any kind of drugs that may lead to significant elevations of dopamine for this population (Meltzer & Stahl, 1976). However, it is worth mentioning that those who are not actively experiencing symptoms may be as much as 40% less likely to experience amphetamine-induced psychosis, and amphetamine-induced psychosis does not usually occur after initial use but rather after prolonged, repeated use (Curran et al., 2018; La Torre et al., in press; Paparelli et al., 2011).

Another major consideration would be the degree to which the PAP protocol offers support, with clinicians ideally being prepared to provide inpatient care, if needed, as well as provide medical interventions as appropriate, i.e., administration of sedatives, and anti-psychotics (La Torre et al., in press). This is because individuals with psychosis may require additional support in the context of PAP compared to other diagnostic groups due to the possibility of destabilization, though the likelihood of this occurrence in the context of PAP remains to be determined. Providing extended supervision after psychedelic dosing sessions is also strongly recommended to ensure integration of such experiences, which is an essential component of PAP (Bathje et al., 2022).

An additional factor to consider is assessing the specific etiological origins or underlying cause(s) of individuals' psychosis. Those whose psychosis may be the result of biological causes such as epilepsy, sleep deprivation, or drug use would not be administered PAP as a form of treatment for these indications, and instead would be offered other non-psychotherapeutic methods such as medical interventions (La Torre et al., in press). Similarly, individuals who appear to be experiencing psychosis but are instead experiencing spiritual emergency may also not require such an intensive form of treatment as PAP, though these groups may be able to use PAP to treat other co-morbid issues.

Additionally, individuals whose mental experiences involve highly paranoid thoughts and inability to form rapport with their therapist may be contraindicated for PAP. This is because the strength of the therapeutic alliance is believed to be of utmost importance in the context of treatment outcomes with PAP, and ability to foster trust, openness, and vulnerability is tantamount (La Torre et al., in press; Murphy et al., 2022). An additional risk of PAP for all populations that must be acknowledged in hallucinogenic persisting perception disorder (HPPD), which is characterized perseverating perceptual distortions that persist after the drug has been metabolized and left the body (Halpern et al., 2018; Lerner et al., 2014).

CHAPTER 2: CANDIDATE ROLE AND CONTRIBUTION IN STUDY 1

Joseph T. La Torre (MTS), the Principal Investigator and Psychology Ph.D. candidate proposing this thesis was the lead researcher in this study. He is responsible for developing the research questions, reviewing the relevant literature, formulating hypotheses, leading ethics application approval, and interviewing the participants of the study. He also led data analysis, interpretation of findings, and writing the manuscript.

The study was formally accepted by the editors of the International Journal of Mental Health and Addictions Psychedelics Special Issue on June 14, 2023, and is currently in press. Publication of the article was initiated through invitation by the editors. The tentative citation is: La Torre J., Mahammadli, M., Greenway, K., Faber, S., & Williams, M. (in press). Expert opinion on psychedelic-assisted psychotherapy for individuals with psychopathological experiences of psychosis and psychotic disorders. *International Journal of Mental Health and Disorders.*

CHAPTER 3: EXPERT OPINION ON PSYCHEDELIC-ASSISTED PSYCHOTHERAPY FOR INDIVIDUALS WITH PSYCHOPATHOLOGICAL EXPERIENCES OF PSYCHOSIS AND PSYCHOTIC DISORDERS

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3.1. Abstract

Background: Currently, individuals with personal or familial histories of psychopathological experiences of psychosis, psychotic spectrum disorders, bipolar disorder and similar conditions are excluded from most psychedelic clinical trials, studies, and treatment programs. This study sought to determine why such an exclusion exists, what the implications of the exclusion criteria are, what a psychedelic therapy protocol could look like for this group, and if there was agreement in expert opinion.

Methods: In-depth interviews with 12 experts in the fields of medicine, mental health, and the effects of psychedelics were conducted in an expert consultation format. Interviews were transcribed and themes, and exemplar quotes were produced using an Interpretative Phenomenological Analysis (IPA) approach.

Results: We found that while the exclusion criteria may be justified for psychedelic protocols that provide minimal psychological support for participants, experts overall agreed that psychedelic-assisted psychotherapy is not necessarily contraindicated for all individuals within this group. Rather, results suggest that psychedelic-assisted psychotherapy, which include high

levels of support, may be of benefit to some individuals experiencing said conditions and symptoms. Potentially relevant factors for predicting treatment outcomes include specific symptom endorsement, illness duration, symptom severity, quality of therapeutic alliance, role of trauma in symptom etiology and perpetuation, and the level of other supports in the client's life.

Keywords: Psychedelic-assisted psychotherapy; MDMA; ketamine; psychosis; schizophrenia

3.2. Introduction

3.2.1. Psychedelic-assisted Psychotherapy

Psychedelic-assisted psychotherapy (PAP) refers to psychotherapy that is centered on dosing sessions that feature the administration of psychoactive compounds known as psychedelics. 'Psychedelic' is a term coined by Humphrey Osmond in 1957 meaning *mind-manifesting* (Swanson, 2018). The primary members of the psychedelic family are known as "classic psychedelics" and include lysergic acid diethylamide (LSD), N,N-dimethyltryptamine (DMT), psilocybin, and 3,4,5-trimethoxyphenethylamine (mescaline). Other compounds that produce experiences like the classic psychedelics and have been studied in the context of PAP are 3,4-methylenedioxymethamphetamine (MDMA) and ketamine. For the purposes of this paper, PAP is defined as psychotherapy that includes the intentional administration of the classic psychedelics as well as MDMA and ketamine due to their abilities to invoke similar empathogenic and mystical experiences (Muscat et al., 2021; Wagner et al., 2017).

3.2.2. Exclusion Criteria for Psychedelic Research and Practice

While individuals with a range of conditions have been asked to participate in psychedelic clinical trials, those with personal or familial histories of psychopathological experiences of psychosis, psychotic spectrum disorders, bipolar disorder, and similar conditions have been historically and remain currently, excluded from research and practice of PAP, despite a lack of evidence demonstrating such treatments cannot be of use to these populations (Arnovitz et al., 2022; clinicaltrials.gov, 2020; Friesen, 2023; Mahmood et al., 2022; Wolf et al., 2022; Ye et al., 2019; Zeifman & Wagner, 2020). Ethnoracially diverse participants have also been

underrepresented in psychedelic studies, demonstrating the need for revising practices to promote greater inclusivity (George et al., 2020; Michaels et al., 2018). Currently MDMA is considered a breakthrough treatment for only those with treatment-resistant posttraumatic stress disorder (TR-PTSD), while psilocybin is being explored primarily for depression (Griffiths et al., 2016; Mithoefer et al., 2019). However, there are far more psychiatric conditions than those being included in psychedelic clinical trials as of 2023, many of which share similar symptomatic clusters, etiologies, and phenomenology, and not all conditions respond well to treatments that are gold-standard, warranting an investigation into whether a broader range of patients could benefit from PAP (Sloshower et al., 2020).

3.2.3. Ketamine for Psychosis

Ketamine has demonstrated multiple avenues of treatment for patients with bipolar disorder and schizophrenia (da Frota Ribeiro et al., 2016; Kraus et al., 2017; Lahti et al., 2001; Martinotti et al., 2023, Ye et al., 2019). For example, the symptoms of depression and suicidal ideation in treatment-resistant bipolar disorder patients have been shown to be reduced within a single day of a subanesthetic intravenous ketamine infusion (Wilkinson et al., 2018). In the context of clinical trials, ketamine is explicitly designated as a treatment for suicidal ideation, as it has been shown to decrease suicidal ideation by 79% while improving cognitive deficits of depression, potentially by increasing neuroplasticity (Calabrese, 2019; Collo & Merlo, 2018). Unipolar and bipolar depression, which can often feature psychotic symptoms, have been effectively treated with ketamine due to its ability to target resistant depression while regulating anxiety, inflammation, and agitation (Lahti et al., 2001). Thus, it is not unrealistic to assume that the compound may be therapeutic for people with similar disorders and symptoms of psychosis for

its ability to enhance awareness, generate novel insights, and promote one's ability to engage in the therapeutic process (Dore et al., 2019). Ketamine is known to be generally safe and effective with a wide variety of psychiatric medications, including serotonin reuptake inhibitors (SSRIs), antidepressants, anxiolytics, antipsychotics, and more (Kraus et al., 2019; Muscat et al., 2021; Rosenbaum et al., 2021).

Studies also show that subanesthetic doses of ketamine in both patients with and without schizophrenia induce a temporary, dose-related altered state commonly referred to as dissociation (da Frota Ribeiro et al., 2016; Kraus et al., 2017). Although there is some debate, many studies suggest that the actual experiences of ketamine-induced "dissociation", which may be better conceptualized as bodily transcendence, underlie its benefits (Niciu et al., 2018). Ketamine-induced dissociation or experiences of material transcendence in patients with schizophrenia is transient, does not appear to result in distress, and resolves within a few hours post-infusion (Krystal et al., 1994; Le et al., 2021; Xu et al., 2016).

Ketamine is also the only psychoactive substance that has been explicitly tested in patients with chronic psychotic conditions since the first wave of psychedelic research. Ye and colleagues (2019) administered low doses of ketamine intravenously to 15 patients with treatment-resistant schizophrenia to treat comorbid depressive symptoms and found there to be transient benefits on mood and no effect on either positive or negative symptoms. Likewise, ketamine has been shown to increase activity in mood processing in several regions of the brain including the mPFC, anterior/posterior cingulate cortex, and angular gyrus, which are known to be significantly inhibited in individuals with schizophrenia (Kotoula et al., 2021).

As a result, it is possible that increasing activity in such regions with the administration of ketamine could reduce schizophrenia-related symptoms and improve mood and affective

processes. At the same time, ketamine has been shown to worsen other psychotic mental health conditions such as schizophrenia in some instances (Lahti, 1995; Lahti et al., 2001). Overall, more research must be carried out to determine when ketamine and ketamine-assisted psychotherapy may be beneficial for individuals with psychotic conditions (Corlett et al., 2016; Pribish et al., 2020).

3.2.4. MDMA for Psychosis

There is reason to believe that psychedelics may be effective in treating PTSD comorbid with certain symptoms of psychosis. One drug whose psychoactive profile bears resemblance to classic psychedelics, which maintains its status as an 'empathogen' is 3,4-methylenedioxy methamphetamine or MDMA. MDMA-assisted psychotherapy as observed in breakthrough treatments for refractory posttraumatic stress disorder (PTSD) may be useful in treating psychotic symptoms with co-occurring trauma due to the two groups sharing similar symptomatic clusters, etiologies, and phenomenology (Mithoefer et al., 2019). More specifically, the drug's ability to create an emotionally safe space to foster enhanced vulnerability with therapists allows for the processing of traumatic memories, putatively by releasing oxytocin and decreasing the activity of the amygdala, thereby reducing the overall response to stress, fear, and anxiety (Kirkpatrick et al., 2014). However, such reasoning is speculative, and more research must be carried out to see if similar processes would occur in individuals with psychotic symptoms (Hartley & Phelps, 2010; Hysek et al., 2013; Mueller et al., 2008). Caution may be warranted with MDMA given that amphetamines are the class of drugs strongly associated with inducing psychotic symptoms (Kalant, 2001).

3.2.5. Psychedelics and Entheogens for Psychosis

Some of the earliest work conducted on psychedelics involved the administration of lysergic acid diethylamide (LSD) to patients with schizophrenia (Friesen, 2022; Fuentes et al., 2020; Rucker et al., 2018). Several articles (reference in Appendix A), discuss the effects of psychedelics on individuals with diagnosed schizophrenia as found by studies during the first wave of psychedelic research. Some of these studies found that mescaline and LSD aggravated symptoms in individuals with schizophrenia such as one study from 1961, which describes 7 of the 14 schizophrenic patients experiencing LSD-induced psychosis at high doses (500μg), while several found psychedelic drug administration to resolve schizophrenia-related symptoms. Nonetheless, we hold it to be unethical to formally cite these articles as they are notoriously some of the most harmful experiments ever conducted in the history of psychology. Many of these articles describe giving drugs such as LSD in extremely high doses such as 2000ug to patients in poor settings (i.e., environments where patients may experience significant discomfort and distress such as being tied down to a hospital bed), despite knowing at the time that psychedelic use in a poor environment often results in challenging experiences (Strauss et al., 2022). Therefore, we encourage readers to refer to our appendix, which offers a critical analysis of such research and emphasizes the need for ethical research practices in the future.

3.2.6. Purpose of the Study

The purpose of this study is to explore opinions about excluding people with a personal or familial history of psychopathological experiences of psychosis and psychotic spectrum disorders, psychotic mood disorders and similar mental health conditions from participating in

psychedelic clinical research and experimental treatments. We asked experts when psychotic disorders and symptoms are justified as an exclusion criterion for psychedelic clinical studies and treatment programs, why and when such a position may be warranted, and what a psychedelic therapy protocol for this group might look like. Several other related topics were discussed.

3.3. Method

3.3.1. Study Design

The study design utilized an expert consultation approach, which involved interviewing participants considered to be experts in the field. Participants were asked specifically about the validity of current exclusion criteria, whether they believed psychedelic-assisted psychotherapy could be effective for individuals with psychopathological experiences of psychosis, and/or psychotic disorders, and if so, how such a study or protocol could be carried out safely and effectively. A range of similar topics were also covered to help answer the main research questions. A total of 12 participants were recruited and questions were based on a semi-structured interview format template (See Box 1).

3.3.2. Sample Size

The sample size of 12 was deemed sufficient due to the specific requirements regarding expertise (e.g., experience, advanced degrees, being recognized experts in the field, etc.), background, and experience. Typically, a sample size of around 20 interviews is considered adequate (Vasileiou et

al., 2018). However, given the highly specialized experiences required, i.e. individuals with backgrounds that would permit them to be considered experts in exploring psychedelic therapy for individuals with psychosis, fewer participants were required to reach saturation (Busetto et al., 2020). Due to the high degree of specificity of knowledge, expertise, and training required to answer the questions involved in the study adequately, sampling was not random, and only known experts with significant experience or interest in working with psychedelic compounds or psychotherapy were contacted to participate.

Box 1: Applicable Interview Questions About Psychedelics and Psychotic Symptoms

PAST CLINICAL EXPERIENCE

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

THEORETICAL

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

3.3.3. Ethical Considerations

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

3.3.4 Qualitative Analysis and Procedures

Recordings of interviews were automatically transcribed using transcription software and subsequently reviewed by two members of the research team for accuracy. Experts' experiences, opinions, and other results were coded using an Interpretative Phenomenological Analysis (IPA) approach (Smith & Osborn, 2015). Major themes and exemplar quotes were identified throughout the transcripts and subsequently coded. Statements that fell under the same theme were synthesized into a narrative that reflected the variety of participants' opinions and were subsequently included in the results section of the paper. Some statements were included in multiple themes if they were relevant to more than one.

3.4. Results

3.4.1. Details About the Expert Participants

The 12 participants we interviewed were all living in the United States and Canada, and are affiliated with several respected institutions, including Johns Hopkins University, California Institute of Integral Studies, Yale University, and University of Toronto. Ten are also affiliated with clinics, hospitals, or are in private practice. Participant selection was deliberate and was based on having expertise in medicine, clinical psychology, psychedelic compounds, and experiences of psychosis. Out of the 12, three participants possessed credentials and experience that demonstrated expertise in all four areas, namely a medical degree combined with substantial clinical experience with individuals with psychosis and psychedelic compounds. One participant possessed area expertise in all three areas except psychosis, three participants possessed expertise in two areas, and three participants of the twelve possessed expertise in one area. Two

participants had lived experience with psychotic-type experiences including having extrasensory abilities, however, did not mention whether they had any formal diagnosis. The mean number of years participants had worked as a healthcare professional was 23 years, out of which 92% had direct experience with the effects of psychedelics. Table 2.1, below, demonstrates the demographic and relevant experience characteristic of the study experts.

Out of the 12 conducted interviews, 9 of the experts were male (66%), while the remaining 3 were female (33%). In addition, 10 (84%) were White and 2 (16%) were people of color. Of the 12, 4 participants (33.3%) identified as sexual minorities. The White male dominant pool of participants is notable and may be attributed to a confluence of interrelated factors including prestige, risk tolerance, racism, and sexism. The gender and racial imbalance within the field may also be due to the continuous presence of sexism, racism, as well as a myriad of challenges in the forms of lacking senior female mentors and familial commitments (Doyle et al., 2016). The imbalanced demographic profile may be further associated with the willingness to participate in risk-presenting activities such as studying psychedelic research, which was both illegal and highly stigmatized until recently. Considering the aspects of legality towards the usage of psychedelics and patterns of risk-taking behavior among males, we would predict a greater quantity of male experts being willing to participate in potentially stigmatizing interviews (Hirschberger et al., 2002; Otufowora et al., 2021).

Table 2.1

List of Experts Interviewed

ID	Gender	Race	Position	Years as a Healthcare Professional	Years of Direct Experience with Psychedelics
1	Male	White	Psychiatrist	7	5
2	Male	White	Clinical Psychologist	17	12
3	Male	White	Psychotherapist	21	7
4	Male	White	Psychiatrist	62	63
5	Male	White	Psychiatrist	53	53
6	Male	Asian	Psychiatrist	5	2
7	Female	White	Psychotherapist	16	5
8	Male	White	General Physician	9	0
9	Female	White	Minister, Spiritual counselor	0	25

10	Male	White	Doctor of Nursing	24	7
11	Male	Hispanic	Physician	18	28
12	Female	White	Doctor of Nursing	44	55
			Total Years:	276	263

3.4.2. Themes

Interviews uncovered a broad consensus surrounding four discrete themes. These included (1) the need for structured guidance that must be established during psychedelic treatments for people with histories of psychotic experiences or diagnoses and other related suggestions, (2) the potential influence of physical and emotional trauma on the development of psychotic symptoms and disorders, (3) the problematic terminology, pathologizing, and stigmatization of psychotic experiences, and (4) inclusion and exclusion criteria for psychedelic treatment. Themes ranged in levels of consensus.

3.4.3. Psychedelic-assisted Psychotherapy for Psychotic Symptoms and Conditions

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

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

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

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

According to the participants' responses, simply identifying whether there is a history of psychotic symptoms or endorsement of psychotic symptom(s) is not as relevant for determining if the individual will be a good candidate for psychedelic-assisted psychotherapy as whether symptoms are distressing, debilitating, or causing life impairment. Experts also stressed the importance of identifying the cause of symptoms, and differentiating whether they are the result of a psychotic spectrum disorder, or another condition such as bipolar disorder. The need to distinguish symptoms of a psychotic disorder from the experiences of a spiritual emergency was also mentioned by two experts. Thus, clinicians should remember the heterogeneous nature of psychotic experiences, differential diagnosis, and similar experiences that resemble psychosis, and assess specific symptom endorsement together with levels of functioning.

As participant 6 said, "Psychotic depression I could imagine psilocybin being useful for in a way that psychotic mania, I just can't," demonstrating how some within this group could be at higher risk than others depending on their specific experience and the need to assess candidacy on a case-by-case basis. It also demonstrates how different compounds could be useful in different situations. In addition, whether symptoms are debilitating must also be considered. While participants mention that psychedelics could certainly be used by individuals with psychotic experiences that are not debilitating, it is also important to note that people on the more severe end of the spectrum may not necessarily be contradicted either. As participant 6 mentioned, "for chronic psychosis, I mean, we have nothing to go on from modern studies about that." Participant 2 also said that eventually we are going to need to test whether psychedelic-assisted therapy could help people with mild, moderate, and severe psychosis. This is because there is not enough data to dismiss the possibility of psychedelic treatment being beneficial to those with chronic psychosis, only fraught data collected during the first wave of psychedelic

research (Strauss et al., 2021; Swanson, 2018).

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

Table 3.2

Verbal Interviewee Responses Regarding Psychedelic-assisted Psychotherapy and Psychopathological Experiences of Psychosis and Psychotic Disorders

Theme	Description	Exemplar quotes
Trauma-Informed Care	Association of experienced trauma and psychotic symptoms	*"It [psychedelic-assisted psychotherapy] can be helpful for people who have a history of trauma"* *"We bring traumatic memories up from the poorly stored locations in the left amygdala. We bring them into an MDMA environment where there are two therapists, who are supporting the person"*
Understandings of Psychotic Symptoms	Systematic reassessment of psychotic diagnoses and treatment protocols	*"These are terms [psychosis] that are over a century old"* *"There should be an ability to build up rapport. Old psychoanalysis would say it is just kind of defined psychosis, as this is somebody that you can't psychoanalyze. They lumped together all of these different conditions"*

Psychotic Symptoms as an Exclusion Criterion	Need to revise, rethink and nuance protocols, nosology, and phenomenology of psychosis	*"For these one-shot situations, I think the exclusion criteria are appropriate"* *"What would be the effects of psychedelics on people who hear voices, who actually don't meet criteria for psychedelics for psychotic disorders? Versus someone who predominantly has delusions versus someone who's more paranoid?"*
Clinical Recommendations	Psychedelic treatment and assessment guidelines for patients with psychotic symptoms	*"I think a huge thing would be family and peer support and community support. If they don't have a strong support network it's more of a concern"* *"You must have a great deal of safeguards in place for the person, including an early trigger for hospitalization and then perhaps the ideal place to treat psychosis; it would be on an inpatient basis"*

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

3.4.4. Trauma-Informed Care

Several participants mentioned the possible benefit of psychedelic-assisted psychotherapy for individuals with trauma connected to their psychotic symptoms. Participant 3 who is a well-known specialist in the treatment of psychotic symptoms and disorders, and has lived experience with psychosis also noted that:

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

They also said that:

> Often when they do the research, they say lots of people have PTSD and psychosis, and they talk about it that way, but then they also talk about trauma seems to make psychosis more likely. In fact, having multiple kinds of trauma...the link between multiple kinds of

> trauma and psychosis is as strong as some of the studies that have found between lung cancer and tobacco" and that, "I think the fact that somebody has lung cancer doesn't mean they smoke. And the fact that somebody has psychosis doesn't mean you're going to find this big prominent history.

Considering participant 6's comment that "MDMA is almost a perfect drug for trauma," the potential role of trauma in psychotic symptom etiology and symptom maintenance may be extremely relevant to understanding why psychedelic interventions may be effective for individuals with psychotic symptoms. Meanwhile participant 4 said that psilocybin could reactive traumatic memories while participants 5 and 6 mention that psilocybin could be helpful.

3.4.5. Understandings of Psychotic Symptoms

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

Participant 6 said that "There are clusters of psychosis that don't look like each other" while participant 1 talked about how "DSM diagnoses are not single disease entities, so not everyone with a diagnosis of schizophrenia is the same." For example, several participants mentioned that some individuals may have paranoid delusions and others hallucinations. Participant 4 said, "psychosis doesn't really tell me anything useful as to what's going to be helpful to the person" and that, "These are terms that are over a century old -- before the car,

before the light bulb." Participant 6 also noted the diversity of psychotic experiences, saying that "One person reporting voices may not be at all the same thing. Like somebody that's saying, 'I hear voices that remind me of the thing that happened' versus somebody that's mumbling to themselves who keeps looking over to the left of the room. You're talking to them, they keep getting distracted; it literally looks like they're hearing something and they're kind of talking back and they're trying not to show you they're doing that. Those are so different. And so lumping them together as like, 'hearing voices' is [not the same]."

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

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

be reduced to a hallucination.

3.4.6. Psychotic Symptoms and Disorders as Exclusion Criteria

Findings indicated that the exclusion criterion barring the participation of people with psychopathological experiences of psychosis and psychotic disorders including psychotic spectrum disorders, psychotic mood disorders, psychotic personality disorders, and other similar conditions from current psychedelic clinical studies designed for PTSD, anxiety, and depression might be justified since they typically do not provide enough support for this especially vulnerable and high-risk population. Participant 5 noted, “It’s not because we fear that psychosis is necessarily contraindicated.” Several other participants echoed this sentiment saying that in a context where there is substantial support in place, psychedelic-assisted interventions could be both safe and effective for the population of interest.

Participant 4 noted that having psychotic symptoms are at times an exclusion criterion in various clinical trials, studies, and treatment programs, which offer psychedelic dosing sessions on an outpatient, short-term basis because the protocols do not offer enough support. For example, a context where such treatment is provided on an inpatient basis and the clinician uses the compound as an adjunctive to long-term supportive psychological work with a person could produce different results from when taken as part of a less supportive program some participants noted. Participant 4 elaborated by saying that the exclusion criteria for less supportive contexts, which provide a “one-shot” or “weekend” experience are justified because “you really don't know what you are going to be dealing with and you don't know how you are going to close or whatever you are going to open.” Participant 7 also mentioned an inpatient context as being effective and that the protocol could be akin to treating substance use disorders.

Participant 1 said that it is probably not true that all people with psychotic symptoms cannot receive psychedelics safely and pointed out that part of the reason for the situation at hand may be due to FDA's criteria requests. On this matter, participant 7 said, "Psychiatrists tend to be quite conservative" and said, "Why should we deny people the opportunity to have those numinous experiences? That's gatekeeping. That seems like really egregious gatekeeping. I think it would, again, be on an individual basis. And why shouldn't we all have the opportunity to have those mystical experiences?"

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

3.4.7. Clinical Recommendations

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

Several participants noted that a strong support system—both inside and outside therapy—would be particularly important. Participant 6 mentioned that in the psychedelic-guide

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

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

Further considerations suggested by participant 8, a general physician, include history of drug use, cardiac history, age (over the age of 24 and 30-65 as ideal) and family history of sudden cardiac death. They also urge assessing for any conditions with an electrolyte panel, signs of infection, current drug usage, presence of tumors, history of homicidal/suicidal ideation, self-harm, presence of weapons at home, and, as mentioned by other participants, social and family support. Furthermore, they discussed pharmacodynamics and kinetics of the drugs the potential participant is using, and the metabolism/excretion of the compound in treatment, noting that if the active component of the drug is a metabolite, and the presence of any kidney or liver disease, which may result in the client not being able to excrete the drug as quickly, which may lead to buildup.

Table 3.3

Verbal Interviewee Responses Regarding Specific Psychedelic Compounds and Psychopathological Experiences of Psychosis and Psychotic Disorders

Theme	Description	Exemplar quotes
MDMA*	Facilitates the processing of traumatic material	*"MDMA are more likely to have positive emotions, so it's not as likely to activate negative memories"* *"MDMA produces this sense of safety that allows people to explore things that otherwise are kind of frightening"*
Ketamine	Use for psychotic symptoms	*"Ketamine is something that does seem less likely to push people into scrambled states"* *"I recognize for one thing, that Ketamine is an abusable drug and it's difficult to abuse serotonergic psychedelics because the brain just won't let you do it"*

Psilocybin	Positive outcomes despite being a challenging experience	*"It was complete torture to this person, and yet they had a complete remission of their depression"* *"Memories are restored, they are altered by the experience of the psychedelic work and are not stored in the same way that they were when they were first done"*
Ayahuasca	Risk of destabilization but may still be therapeutic	*"Ayahuasca is on the heavy-duty side of triggering such episodes [psychosis], versus MDMA that is maybe a little more mellow. Ayahuasca, is a high risk"* *"We had this guy who was hospitalized post-ayahuasca and he still thinks it was the best thing that ever happened to him"*
Serotonergic drugs	LSD/Psilocybin/combinations	*"MDMA is an introductory molecule to modify the psychotic state, then I would use psilocybin or possibly combination of the two"*

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

3.4.8. MDMA

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

psychotic symptoms.

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

Participant 6 mentioned that MDMA “is almost a perfect drug for trauma in a way that I don't think psilocybin is” and that “MDMA produces this sense of safety that allows people to explore things that otherwise are kind of frightening.” However, when asked about the compatibility of psychedelics and psychotic symptoms, went on to say that “it depends on what we're talking about, but somebody who is acutely psychotic...like they're hallucinating, they have delusions, they’re thought disordered….I don't think I could in good conscience give them MDMA.” Participant 12 also mentioned that “MDMA is in a kind of middle category between [serotonergics and ketamine]” and that it too has the potential to be abused.

3.4.9. Ketamine

Two participants mentioned ketamine, one believing that it could be of benefit to the population of interest, and another pointing to its tendency to be abused. Participant 11 explained that ketamine may be significantly safer as a compound that seems “less likely to push people into

scrambled states." When asked about the clinical profiles of specific compounds, participant 12 mentioned that ketamine is an abusable drug. They did not necessarily say this was a good or bad thing or specific to psychotic symptoms, but simply that there is capacity to abuse, which nuances the clinical profile of the drug, namely safety.

3.4.10. Psychedelics and Entheogens

When asked if entheogens like psilocybin are less relevant than empathogens, they responded, "Not less relevant. I think just, I would imagine it's easier to go wrong. Maybe it's like a high risk, high reward situation." Participant 4 echoed this sentiment stating that psilocybin could reactivate traumatic memories, though participants 5 and 6 also mentioned scenarios where psilocybin might be effective. Participant 11 also noted that Ayahuasca may be the most likely to cause problems for a person with a history of psychotic symptoms. Specific combinations such as MDMA and psilocybin were also mentioned as being of potential therapeutic benefit.

3.5. Discussion

This study has collected and distilled the opinions and recommendations of the experts, who conclude that individuals with personal and familial histories of psychopathological experiences of psychosis and psychotic disorders do not always have to be excluded from PAP. However, if such treatment should be considered, it must be tailored to the population by providing extensive support and supportive psychotherapy. Other possible risks must also be considered however, such as if PAP is not conducted in a highly supportive context, exclusion is justifiable, but to exclude people with all types of psychotic symptoms from all psychedelic treatment and studies may be erroneous. Overall, there is tremendous heterogeneity in psychotic experiences, and candidacy should be evaluated on an individual basis as the literature strongly suggests

variegated etiology of psychotic conditions and symptoms. For example, individuals whose psychotic experiences may be a result of a psychopathology such as a psychotic spectrum disorder, mood disorder, personality disorder and/or other similar conditions may be more appropriate to include in psychedelic clinical research than those whose psychotic experiences are a result of epilepsy, spiritual emergency, or drug-induced psychosis, which would all likely be resolved with other treatment options, or in some cases, spontaneously.

Overall, with the right candidates and under the right conditions, patients seeking psychedelic-assisted therapy who also have signs of psychotic symptoms resulting from the conditions of interest with a history of trauma may constitute a pioneer class of patients that could receive this treatment either as compassionate use or off-label patients. At the same time, if individuals from this population are invited to participate in psychedelic clinical research, it would be extremely important to not make the same mistakes that occurred during the first wave of psychedelic research (see Appendix A) including heinous research abuses and to uphold gold-standard scientific methodology (Strauss et al., 2022).

3.5.1. Why Ask Experts

Interviewing experts was an effective strategy for gathering information around psychedelics and psychotic disorders and symptoms. No modern clinical studies have been conducted on the topic of expert beliefs regarding the effectiveness, safety, and risk of PAP for people with psychopathological experiences of psychosis and/or psychotic disorders. This reflects a broader trend in psychiatry where clinical study populations are often unrepresentative of real-world patient diversity and severity. Mainstream opinion appears to be based on assumptions formed during the first wave of psychedelic research, when an abundance of abuse was carried out on vulnerable hospitalized persons, often with chronic schizophrenia (Strauss et al., 2021).

Empaneling a group of experts on psychedelics and psychiatry provided clinical perspectives grounded in experience and expertise which has provided more informed recommendations.

3.5.2. Alignment with Prevailing Approaches

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

Individuals with mental health conditions have historically not only been unable to access promising experimental treatment due to a variety of barriers while also having been repeatedly subjected to inhumane experimentation (Campbell & Williams, 2021; Strauss et al., 2021). Both have been true for PAP. If equity is to be achieved, this must necessarily extend to individuals with mental health conditions being able to have access to experimental and promising psychedelic breakthrough treatments that are currently being demonstrated to be both highly efficacious and safe in clinical trials (Campbell & Williams, 2021). This is a matter of psychiatry

advancing its ethics by taking a cue from other fields that have allowed patients access to innovative treatments such as experimental drugs for cancer and infectious diseases. While excluding some patients with some forms of psychotic symptoms from psychedelic research may be justifiable if their conditions would result in significant safety risk, excluding all individuals with psychotic symptoms is likely more reflective of inequities and biases in psychiatric research rather than legitimate safety concerns. As data from the study indicate, there are individuals with symptoms of psychosis who would like to try psychedelic-assisted treatment but are denied the opportunity. There are also those who, despite being denied access, use underground psychedelic treatment to their benefit or peril.

3.5.3. Next Steps in Investigating the Issue Further

More research must be done to create potential pathways for those with psychopathological experiences of psychosis and psychotic disorders to benefit from psychedelics, and an initial pilot trial, which has these forms of psychotic symptoms as specific inclusion criteria would be an ideal opportunity to gather more empirical data to support the hypotheses the experts suggested. This study would need to incorporate the various clinical recommendations given by the experts and proceed with caution by ensuring the proper safeguards are put in place. In addition, stratification by cause of psychotic symptoms (e.g., genetic, environmental) and whether symptoms emerge because of epilepsy, or another related medical condition rather than psychopathology should be incorporated in any trial design. Findings from this study also indicate that individuals with a documented history of psychotic symptoms related to experiences of trauma may be better candidates for inclusion than those who may have psychotic symptoms

from other causes. Likewise, people with mild or transient psychotic symptoms because of psychopathology might be better candidates than those persistent and severe symptoms. Targeting psychedelic treatment of underlying psychotic symptoms in conditions such as bipolar, depression, and PTSD may also provide insight into psychedelic mechanisms of actions of psychedelics more broadly.

3.6. Study Limitations

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

Another limitation is the lack of ethnic and racial diversity of participants. As we attempt to analyze the use of psychedelics while upholding demographic diversity among our participants, we stumble upon several physical and mental barriers. Specifically, one barrier while participating as a racialized person, is a stigmatizing social environment that discourages many from joining psychedelic studies as participants and researchers (George et al., 2020; Michaels et al., 2018). Targeting race demographics, where 84% of the interviewees identified as White directs us towards the officially acknowledged presence of structural racism in the field of psychiatry (American Psychiatric Association, 2020). With only 3.3% of the psychiatrists being

Black, despite the 13.4% Black population in the U.S, the effects of historical as well as current racial discrimination are apparent (U.S. Census Bureau, 2019; Peckham, 2017). The increasingly cascading factors of education disparities and financial challenges, stacked on top of the racial biases silence the voices of marginalized communities (AAMC, 2018; Arciniegas, 2015). In addition, we suspect that the trend that naturalistic users of psychedelics being mostly White, and male may have a direct impact on this population being more likely to enter the field as professionals (NSDUH, 2020).

It is also worth noting that the results may have been influenced by the selection of experts, which, although intentionally diverse, was not technically random. Instead, experts were recruited based on their reputation in the field, knowledge, and background. Some individuals, due to their eminence, were unable to participate directly and referred others for interviewing and while this did not make the process random, it did introduce some novelty to the selection process. Furthermore, other factors that may have influenced the findings was that diversity in background, experience, and demographics were prioritized rather than specifically diversity of opinion. This was in part because participants' opinions regarding psychedelic drugs and psychotic experiences were not known until the interviews occurred, which may have limited the sampling of diverse perspective.

3.7. Conclusion

Experts overall agree that research can be done to determine how those with psychotic experiences and disorders may benefit from PAP. However, they also stress that not everyone will respond the same, or even similarly, and outcomes depend on both variability at the

individual, personality-level, as well as the way in which the psychotic symptoms developed. Findings from this study suggest that candidates who have a history of trauma, have symptoms that are less severe/chronic, are open and interested in psychedelic medicine, fulfill medical requirements, can form a strong relationship with the therapist, and are not actively paranoid or otherwise destabilized may be among those who respond best to psychedelic treatment within this population. The experts agree that psychedelic use may not be contraindicated for everyone with psychotic disorders and symptoms, but rather a number of supports, precautions, and specific conditions are needed to safely and effectively provide PAP to people with symptoms of psychosis resulting from conditions like first episode psychosis, schizophrenia, borderline personality disorder, bipolar disorder, and similar psychotic-type conditions.

CHAPTER 4: CANDIDATE ROLE AND CONTRIBUTION FOR STUDY B

Joseph T. La Torre (MTS), the Principal Investigator and Psychology Ph.D. candidate submitting this thesis led this study. He is responsible for designing and proposing the study, taking a lead role creating, submitting, and revising the research ethics application, and reviewing pertinent literature. He consulted experts for their feedback regarding methodology, crafted the hypotheses, and took lead roles in data collection, data analysis, and interpreting the findings. Additionally, he led the development of the manuscript. The manuscript is currently being prepared for submission to a peer-reviewed journal.

CHAPTER 5: A QUALITATIVE ANALYSIS OF RETROSPECTIVE SURVEY REPORTS OF EFFECTS OF PSYCHEDELIC USE AMONG INDIVIDUALS WITH PSYCHOTIC EXPERIENCES AND CONDITIONS: MOST DESCRIBE MYSTICAL-TYPE EXPERIENCES AND PERSONAL GROWTH

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5.1. Abstract

Background: Individuals with a history of psychotic symptoms and disorders, as well as bipolar disorder, and other disorders with psychotic features, tend to be excluded from psychedelic-assisted psychotherapy clinical trials and treatment programs. This is in part because it is widely assumed that this population cannot safely use psychedelic compounds due to risk of symptom exacerbation, heightened risk of psychedelic-induced psychosis, and increased likelihood of experiencing adverse reactions, despite minimal research having been conducted on this topic.
Methods: We designed an online, retrospective, phenomenological survey that asked people with psychotic experiences and/or diagnoses (n=100) to report and describe one memorable psychedelic experience, their mental health histories, dose used, set and setting, and other relevant variables including whether they mixed their psychedelic with other substances. We also asked respondents to complete pertinent psychometric questionnaires and answer questions regarding the impact of their psychedelic experience on their well-being, mental health, relationships, spiritual beliefs, and other variables of interest. Thematic inductive analysis was

used to identify recurring themes.

Results: Most respondents (n=88) stated that their psychedelic experience resulted in some degree of personal growth. Many also described mystical-type experiences, increased levels of contemplation and spirituality, improved insight, symptomatic improvements, and feelings of love and appreciation following the experience. Most described overall positive experiences, however, 11% (n=11) described overall negative experiences, which included symptom exacerbation, dysphoria, and terror, and a slightly larger portion described mixed-type experiences.

Keywords: Psychedelic-assisted psychotherapy; psychosis; schizophrenia; bipolar; psilocybin

5.2. Introduction

5.2.1. Historical Exclusion of Those with Psychotic Conditions

Individuals with histories of psychotic experiences and conditions are regularly excluded from clinical studies with psychedelic compounds. To understand why, it is crucial to revisit the first wave of psychedelic research—a time characterized by a fervent pursuit of researching how psychedelics could assist in psychotherapeutic processes during the 1950s and 1960s until the War on Drugs called such research to a close. While a great deal of scholarship and research was produced, including trials examining LSD therapy for individuals with substance use disorder and schizophrenia, research during this time was conducted without scientific rigor (see Appendix A). Studies often lacked standard methodological elements such as being double-blind, incorporating psychometric testing, and control groups (Rucker et al., 2018). Furthermore, many of these trials were unethical.

They followed no proper structure regarding dosage, frequency of administration, nor provided follow-up care, which is highly important to consider when using psychedelics. Many early experiments were also conducted on unwilling participants, namely BIPOC who were incarcerated, as well as people hospitalized for psychotic disorders (Dore et al., 2019; Strauss et al., 2022). Additionally, it was during this time that psychedelics were modeled as 'psychotomimetic', or drugs that mimic psychotic symptoms in users, which in turn led to the idea that individuals with histories of psychosis may experience symptomatic exacerbation as a result of psychedelic drug administration (Swanson, 2018). However, the War on Drugs may have held the most significance in preventing the scientific pursuit of exploring psychedelic therapy for individuals with psychotic disorders by claiming that dangerous drugs such as LSD cause people to go "insane" (Carhart-Harris & Goodwin, 2017; Friesen, 2022).

Current understanding dictates that a personal or family history of psychotic experiences and/or disorders are also considered exclusionary criteria because of the notion that psychedelics exacerbate or catalyze psychotic symptoms in those individuals, despite modern findings demonstrating this (La Torre et al., in press). It is possible that upon testing these hypotheses, it will be found that many individuals with psychotic conditions and experiences could benefit from psychedelic therapy. It is worth noting that in some Indigenous contexts, people with psychotic tendencies partake in psychedelic plant ceremonies (Bathje et al., 2022). They may also even hold roles as shamans and ceremony leaders due to the belief that such individuals hold unique spiritual abilities, rather than being seen as pathologically ill like in Western society (Winkelman, 2021).

It is important to acknowledge the impact of excluding people with psychotic conditions may from psychedelic research negatively affects several highly vulnerable communities including individuals who have psychotic disorders co-morbid with difficult-to-treat anxiety, depression, PTSD, and other problems. While PAP may be able to resolve many other symptoms these individuals have, the presence or potentiality having a concurrent psychotic disorder makes it unlikely for them to be enrolled in psychedelic clinical research. Considering that Black and Latinx Americans are overdiagnosed with psychotic disorders at a rate twice that of White Americans, it goes without saying that such exclusion criteria also have detrimental impacts on BIPOC communities (Akinhanmi et al., 2018; Faber et al., 2023; Muroff et al., 2008). Indeed, it is highly likely that this overdiagnosis is one of the many contributing factors that plays a significant role in the demographic imbalance being observed in psychedelic research today alongside racial bias, and barriers created by systemic racism (Gran-Ruaz et al., 2022; Jacob et al., 2023; Williams, 2020).

5.2.2. Psychedelic-assisted Psychotherapy and Psychotic Conditions

An investigation into the potential role of PAP in treating mental health conditions requires an examination of the causes of such problems. As PAP has been hypothesized to be an effective tool for treating root causes like psychological and emotional trauma, this is one area that is worth exploring in relation to psychosis and psychotic disorders (Feduccia & Mithoefer, 2018). A review of the literature reveals that relationship between psychosis and unresolved traumatic experiences, particularly child abuse, has been well established. According to a study by Read (2001), child abuse was significantly associated with hallucinations. Linear regression analysis revealed that child abuse alone or in combination with adult abuse predicted hallucinations, delusions, and thought disorders. The severity of psychotic symptoms has also been found to have a dose-response relationship with abuse or trauma (Ered & Ellman, 2019). Therefore, if childhood abuse and trauma is likely to have a significant impact on the development of schizophrenia symptoms, then it follows that PAP may be an important option in treating individuals with a history of psychotic disorders and trauma, which may be causally related.

While MDMA-assisted psychotherapy is predominately indicated for those with PTSD, Arnovitz and peers (2022) argue that it may also be used to treat negative symptoms of schizophrenia caused by decreased dopamine transmission. Their rationale is that MDMA targets social functioning and reward processing systems, areas often impacted by negative symptoms, and should be considered a viable treatment option for this diagnostic group. Similarly, a paper by Mahmood and colleagues (2022) suggests that psychedelics could help people with psychotic disorders like schizophrenia by inducing downstream neurophysiological changes and synaptic

plasticity ultimately modifying behavior and cognition. Morton and colleagues (2022) investigated psilocybin use in individuals with bipolar disorder, finding that therapeutic effects are common and that adverse effects are rare. DellaCrosse and colleagues (2022) conducted more analyses on these data and found themes related to positive outcomes. Zeifman and Wagner (2020) explored using psychedelics as treatment for borderline personality disorder (BPD) and suggested that psychedelics can help with BPD's emotional dysregulation while also increasing mindfulness and self-compassion.

Ye and colleagues (2019) investigated the use of ketamine for depressive symptoms in cases of treatment-resistant schizophrenia with comorbid treatment-resistant depressive symptoms and found that ketamine helped to alleviate depressive symptoms without exacerbating psychotic symptoms, although results only lasted one week for most participants. In 2023, Wolf and colleagues expanded on this and described psychedelics' ability to enhance neuroplasticity, postulating that these unique properties may reduce negative symptoms of schizophrenia caused by cell loss and cortical atrophy, giving credence to the possibility of psychedelic-assisted psychotherapy being a viable treatment option for those with psychotic disorders. They also suggested using non-hallucinogenic alternatives, sub-psychedelic dosages, microdosing, or blocking 5-HT2A receptors simultaneously to avoid exacerbating symptoms of schizophrenia or inducing psychosis while maintaining the positive benefits of psychedelics. However, while ketamine may induce antidepressant effects and reduce antisocial symptoms, it can also amplify psychotic symptoms in individuals with a history of psychosis (Da Frota Ribeiro et al., 2016; Le et al., 2021).

Thus, some research is finally being conducted regarding the possible risks and benefits of psychedelic therapy for individuals with psychotic disorders. However, it is important to note

that most studies, apart from research involving ketamine, have been theoretical. Prior to this study, no modern research has explored how individuals with lived experiences of psychosis and psychotic disorders report and describe their experiences of psychedelic use.

5.3. Methodology

5.3.1. Study Design

The study employed a cross-sectional, retrospective, phenomenological survey design that utilized a participatory methodology to collect quantitative and qualitative data. Recruitment included posting recruitment ads specifying the study's purpose, inclusion, and exclusion criteria and occurred over approximately nine months. Following collection, data was cleaned and analyzed using thematic inductive content analysis to produce themes and narratives, exemplary vignettes, and case studies. Statistical observations that captured relevant data regarding changes or lack of changes after psychedelic use regarding drug use, growth, cognition, spirituality, and behavior were also reported.

5.3.2. Sample Size

The sample of 100 individuals was sufficient for the study at hand, which was an initial, preclinical, exploratory topic in a novel area. While conventional survey studies often utilize significantly larger samples, because this study is the first of its kind, focused on qualitative data with quantitative data as supplemental information, and considering the high specificity of the inclusion requirements of the sample, a smaller sample size was appropriate (Busetto et al., 2020). Multiple factors were considered prior to data collection, including data saturation to ensure representation from a diverse range of demographic backgrounds, diagnoses,

psychological experiences, drug use histories, psychedelic experiences and more. Another major factor that was taken into consideration was the desire for more convincing and robust results to answer qualitative research questions. The topic of psychedelic use among individuals with experiences of psychosis and psychotic disorders is complex and a larger sample size was perceived to be important to achieve more robust and generalizable results. Thus, although some aspects of data saturation appeared to be reach before the sample size of 100 was obtained, such as evidence demonstrating themes such as positive, negative, and mixed experiences, data collection did not cease in order to generate greater reliability of results.

5.3.3. Procedure

Participants in the study were recruited from various social media platforms such as Instagram, Facebook, and TikTok, with the primary source being Reddit, and more specifically, Reddit sub-communities (also known as 'subreddits') focused on distinctive themes related to psychotic disorders or symptoms, psilocybin, LSD, and other relevant topics. Recruitment ads with a characterization of the study goals, inclusion and exclusion requirements such as having a disorder that features psychotic symptoms such as bipolar disorder, psychotic depression, psychotic personality disorders, or experiences that resemble symptoms such as perceptual distortions, and psychotic experiences and a link to a Qualtrics™ (Provo, USA) survey were posted regularly and frequently. Upon clicking the link, participants were asked to provide informed consent that had to be affirmed before proceeding. If respondents indicated that they were not at least 18 years old, never diagnosed with a psychotic disorder or reported a history of psychotic experiences, or never had at least one psychedelic experience, they were not permitted to participate in the survey and were redirected to a page thanking them for their time and

explaining their ineligibility to participate. When participants met criteria, they were asked to report demographic information, mental health history, information regarding their psychedelic use, phenomenological information such as mystical elements of their experience, and other variables of interest such as dose, features of their set and setting, etc. More specifically, using a survey from Williams and colleagues (2021) as a template, the survey asked participants to keep in mind one memorable psychedelic experience and complete the survey with this experience in mind. Upon data collection, the research team met regularly to clean the dataset, and perform analyses (approved ethics file number: H-03-22-7959).

5.3.4. Analysis

The methodology of this paper is a qualitative approach with statistical observations as supplemental information. Qualitative analyses utilized an inductive content approach centered on inductive thematic analysis (Elo & Kyngäs, 2008; Hsieh & Shannon, 2005). With this approach, respondent data were examined, and common themes were produced to understand patterns in reports. The analytical procedure ensured that at least two researchers independently coded respondent statements for accuracy, and exemplar quotes, thematic titles, and descriptions that best represented the overall sample were selected collectively and subsequently placed into table format.

Throughout the process of analysis and coding, research assistants (JG, MM, and DZ) met regularly with the Principal Investigator (JL) to discuss agreement and disagreement regarding overarching themes, exemplar quotes, suitability of vignettes, and broader categories. Reaching consensus regarding analyses was a dialectical endeavor that involved careful examination of the dataset and in-depth discussions of participant responses. To ensure validity,

coding guidelines were established following a preliminary review of the data, during which potential themes were identified. Independent cross-checking was also built into the process with at least one research member independently reviewing results. Data saturation was informed by two models: theoretical saturation and inductive thematic saturation. No novel themes appeared after the second phase of data collection and so recruitment ended (Saunders et al., 2018).

The first data analysis centered on open response question asking if the reported psychedelic experience resulted in personal growth and involved identified recurring themes (see Table 5.3). Meanwhile, the open-response question asking participants how they would describe their overall psychedelic experience was used for the second analysis, which featured vignettes (see Tables 5.4-5.6). Additionally, a holistic overview of entire survey reports was used for case studies (see Table 5.7) and categories from the second analysis (overall positive, mixed-type, and negative experiences) were used to inform selection of cases studies. This comprehensive review was implemented to capture the nuanced and complex narratives reported by participants.

Reported statistical observations were selected based on relevance to the research questions, namely what proportion of individuals reported personal growth due to their psychedelic experience, distributions and averages of pertinent measures, percentage of individuals who were comfortable vs. uncomfortable in their environment during their experience, diagnostic data, and reported drug use. Other relevant scores and quantitative data indicative of changes in cognition, spirituality, and behavior are also reported. Frequency of adverse events were reported based on open-ended qualitative responses throughout the survey.

5.3.5. Measures

The survey comprised items from multiple validated tools, including a survey developed for investigating psychedelic experiences among individuals with racial trauma by Williams et al. (2021), select items from the Mystical Experiences Questionnaire-30 question (MEQ-30; Pahnke, 1963), and the Community Assessment of Psychic Experiences (CAPE-42; Stefanis et al., 2002).

5.3.5.1. Psychedelic Use Survey

This survey was developed by Williams and colleagues (2021) to understand how BIPOC use psychedelics to treat racial stress and trauma. The questionnaire asks about psychopathology experienced by the responders and how psychedelics may have impacted psychological and emotional well-being. The survey begins by asking the respondent to hold in their mind a single memorable psychedelic experience, and then to answer questions related to the type of psychedelic taken, dosage, and method of consumption, followed by questions about other substances that individuals may have been under the influence of at the same time either prescribed or recreationally. It also includes items to collect basic demographic information such as gender, sexual orientation, race, ethnicity, and religious beliefs. The measure was adapted for this study to inquire specifically about histories of psychotic experiences, such as whether participants were actively psychotic at the time of psychedelic use, if a history of trauma was present, and what prescription medications they were taking, if any, at the time of their experience. It was also used to collect data regarding respondents' psychedelic drug use such as dose, route of administration, and duration of experience.

5.3.5.2. Mystical Experiences Questionnaire-30 (MEQ-30)

The study implemented a condensed 11-item version of the Mystical Experience Questionnaire (MEQ-30; Pahnke, 1963), a measure that has been validated to evaluate the phenomenology of feelings, thoughts, and observations related to mystical-type psychedelic experiences in research (Griffiths et al., 2006). It is organized into four domains: mystical, positive mood, time and space distortion, and ineffability. Each item is scored on a five-point Likert scale ranging from 0 (none or not at all) to 5 (extreme or more than any other time in life), and the overall score is calculated by averaging the sum of responses. A higher score on the MEQ-30 suggests an intense mystical experience, which has been linked to positive outcomes in the context of psychedelic treatment (Barrett et al., 2015). To enhance participant comprehension and reduce survey duration, slight modifications were made to the wording of the MEQ-30 items. For instance, "Loss of your usual sense of time" was adapted to "I lost my sense of time." Furthermore, only a subset of items was used from each of the four factors. Additionally, the Likert scale was modified to a ten-point scale for greater sensitivity to variations in participant responses.

5.3.5.3. Community Assessment of Psychic Experiences (CAPE-42)

The Community Assessment of Psychic Experiences (CAPE-42; Stefanis et al., 2002) is a validated psychometric tool that explores psychotic-like experiences in a self-report fashion. The survey consists of 20 questions regarding positive symptoms of psychosis, and 22 questions related to negative and depressive symptoms for a total of 42 questions. When a question about the presence of an experience is answered in the affirmative, there is a follow-up question probing for distress levels related to that specific experience (not distressed to very distressed) and symptom frequency (never to nearly always). Frequency and distress scores can be calculated for each symptom dimension (e.g., hallucinations, delusional, and negative symptoms)

along with an overall CAPE-42 score by summing all items. The CAPE-42 was not completed by the entire sample as its use was discontinued upon recognizing that it was highly time-consuming, and a short 7-item psychotic experience checklist took its place. The revised survey was completed by participants 1-59 in the dataset, and the first iteration was completed by participants 60-100.

Table 5.1

Questions from the CAPE-42 to Identify Possible Psychotic Experiences

Symptom Category	Sub-category	Selected Questions
Delusions	Perceptual Delusions	*Do you ever feel as if things in magazines or on TV were written especially for you?*
		Do you ever feel as if some people are not what they seem to be?
		Do you ever feel as if there is a conspiracy against you?
		Do you ever feel that a double has taken the place of a family member, friend, or acquaintance?
	Ideas of Reference	*Do you ever feel as if people seem to drop hints about you or say things with a double meaning?*
		Do you ever feel that you are being persecuted in some way?
		Do you ever think that people can communicate telepathically?
	Grandiose Delusions	Do *you ever feel as if you are destined to be someone very important?*
		Do you ever feel that you are a very special or unusual person?
		Do you ever feel as if the thoughts in your head are being taken away from you?
		Do you ever feel as if the thoughts in your head are not your own?
Negative Symptoms		*Do you ever feel that you are not a very animated person?*
		Do you ever feel that your emotions are blunted?
		Do you ever feel that you have no interest in being with other people?

		Do you ever feel that your mind is empty?
Hallucinations	Auditory Hallucinations	*Do you ever hear your own thoughts being echoed back to you?*
		Do you ever hear voices when you are alone?
		Do you ever hear voices talking to each other when you are alone?
	Visual Hallucinations	*Do you ever see objects, people, or animals that other people cannot see?*

Table 5.2

7-Item Symptoms Checklist to Identify Psychotic Symptoms

Symptom Category	Selected Questions (Yes or No Response)
Hallucinations	1. *Hear voices or see things other people do not* 2. *Smell or feel things other people do not*
Delusions	3. *Feel as if you are an extremely important or special person* 4. *Feel as if others are conspiring or plotting against you or that people are out to get you* 5. *Feel as if you can read other people's minds or that they can read yours* 6. *Feel as if ordinary things such as a song on the radio or a billboard are speaking to you*
Negative Symptoms	7. *Feel as if you are disconnected or detached from your body*

5.3.6. Survey Variations

The present study utilized two slight variations to collect data from participants. Specifically, the CAPE-42 psychotic experience questionnaire was discontinued in the second version of the survey, as it was highly time-consuming and contained several items that were not clearly indicative of psychotic experiences such as having spiritual beliefs and feeling low mood. Rather than using CAPE-42 items to detect psychotic experiences, a short 7-item checklist of typical psychotic experiences was provided for respondents to select from instead. The improved survey also asked participants about their reason(s) for taking the psychedelic, whether they were experiencing an actively psychotic episode at the time of dosing, the state of their symptoms during the psychedelic experience, whether they got better or worse, how they felt immediately after the experience, and relevant details. The survey also included a range of minor revisions, such as allowing participants to skip any item they wished and changing some wording for clarity and specificity. These changes significantly reduced the time required to complete the

survey from 45-60 minutes to 15-20 minutes. The first survey was online for 5 days while the final survey was active for several months.

5.3.7. Data cleaning

Any survey that took less than 90 seconds was immediately removed from the dataset as we expected that any participant completing the survey within this time may not have responded accurately. Next, we removed any participant who did not complete a significant portion of the survey, which was approximately less than 70% as the most important questions in the survey, i.e., those related to phenomenological effects of the psychedelic taken, behavioral changes that may have occurred, MEQ scores, etc., took place after the half-way point of the survey. No remaining participant took less than 8 minutes to complete the survey. Participants who did not report psychotic experience as operationalized in the study or psychotic condition were removed from the dataset. Psychotic diagnoses based on DSM-5 criteria and were coded and categorized as PSD (Psychotic Spectrum Disorder), PMD (Psychotic Mood Disorder), PPD (Psychotic Personality Disorder), OPD (Other Psychotic-like Disorder), and UPD (Unspecified Psychotic Disorder). 'PSD' included First Episode Psychosis, Brief Psychosis, Drug-induced Psychosis, and Schizophrenia. 'PMD' included Major Depressive Disorder with Psychotic Features and Bipolar Disorder. 'PPD' included Schizoaffective Personality Disorder, Schizotypal Personality Disorder and Borderline Personality Disorder. 'OPD' included diagnoses that were not mentioned above but featured psychotic-like experiences such as hallucinations, derealization, and other similar experiences. Also coded as 'OPD' were responses that stated their diagnosis was 'Psychosis Not Otherwise Specified.' 'UPD' included any response that said they were diagnosed with a Psychotic Disorder but did not select which one or provide a specified

diagnosis. Few participants completed the survey with blatant inconsistencies and/or nonsensical entries. These and similar entries were also deleted during the cleaning process. In addition, responses to the survey question asking about dose were adjusted based on the guidelines: For LSD, this was 100ug or below as 'low'; 200ug as 'medium'; and 300ug+ as 'high.' For psilocybin mushrooms this was 1-2g as 'low'; 2.1-3.5g as 'medium'; and 3.5g+ as 'high'. 8% of the sample did not clearly specify their dose and 3% did not provide an answer regarding their dose.

5.4. Results

5.4.1. Participants

The study consisted of 100 respondents (see Appendices B and C for more details). Details pertaining to participant demographics and mental health histories were reported as follows:

Figure 5.1

Ethnoracial Identity of Participants

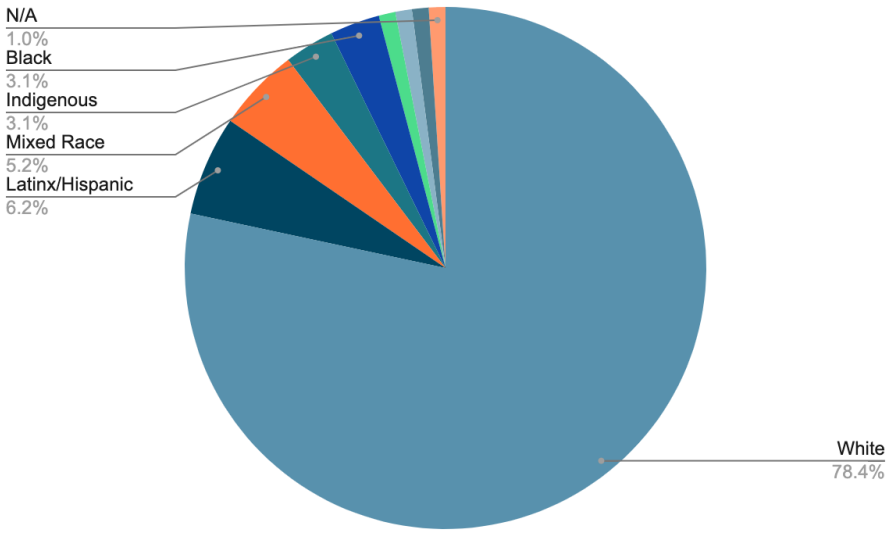


Figure 5.2

Gender Identity of Participants

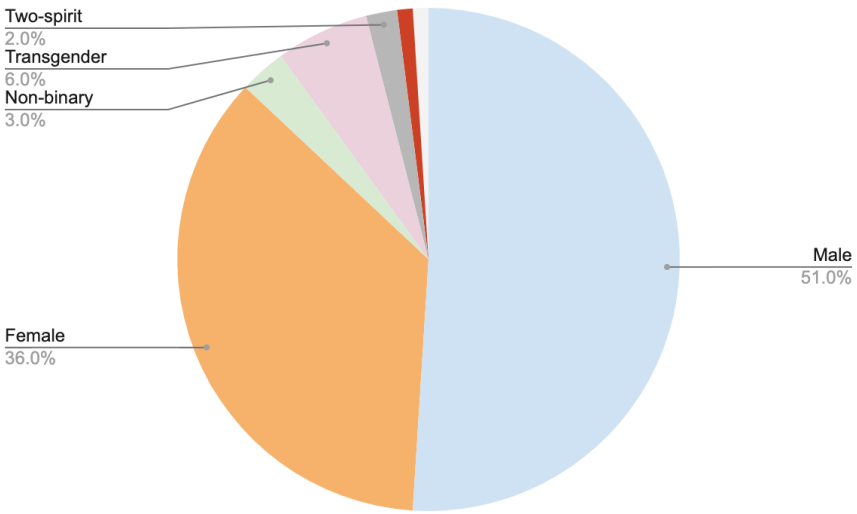
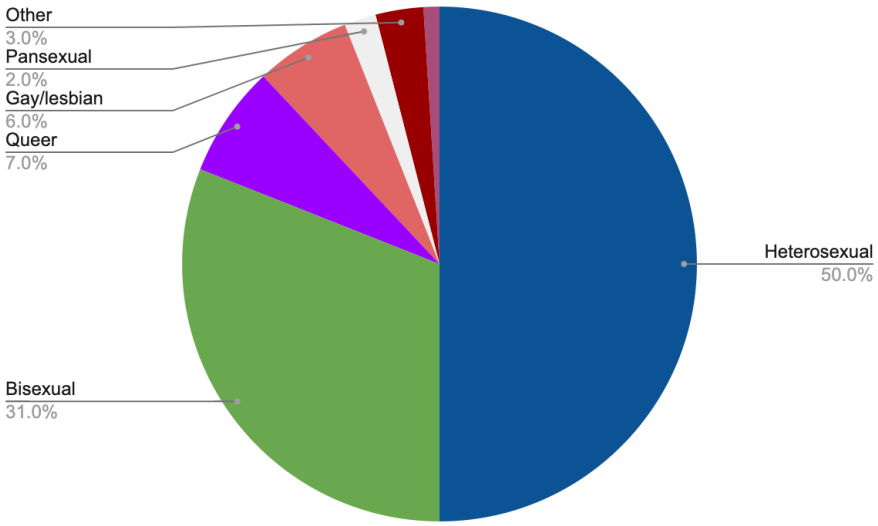


Figure 5.3

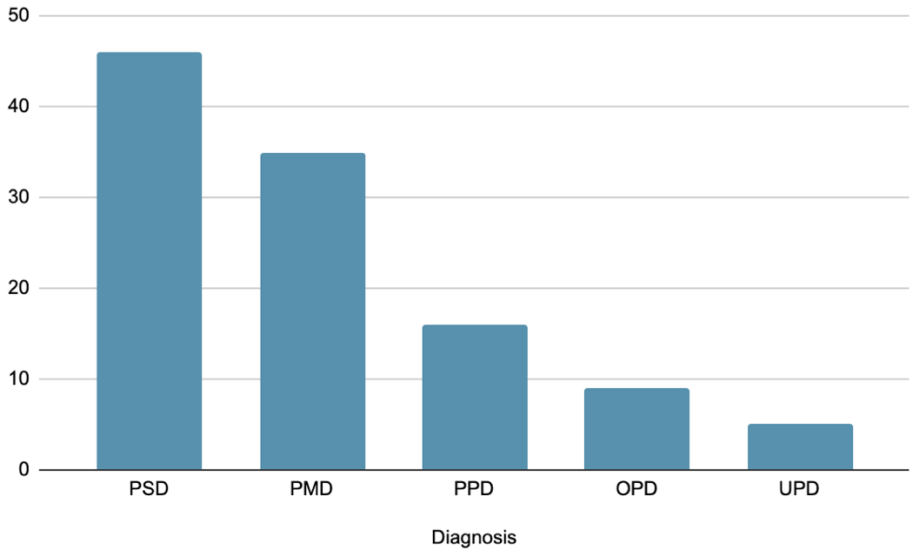
Sexual Orientation of Participants



The following figure illustrates participant reports of psychotic diagnoses or disorders that feature psychotic symptoms. The categories are as follows: Psychotic Spectrum Disorder (PSD) such as schizophrenia, first-episode/brief psychosis, and psychosis not otherwise stated; Psychotic Mood Disorder (PMD) as defined specifically as bipolar disorder or major depressive disorder with psychotic symptoms; Psychotic Personality Disorder (PPD) such as schizoaffective or schizotypal personality disorder; Other Psychotic Disorder (OPD) not mentioned above such as dissociative disorders and Unspecified Psychotic Disorder (UPD) when participants selected 'psychotic disorder' but did not clarify which they were diagnosed with. It is important to note that not all respondents were diagnosed with a psychotic disorder, and at the same time, some participants endorsed having more than one psychotic disorder.

Figure 5.4

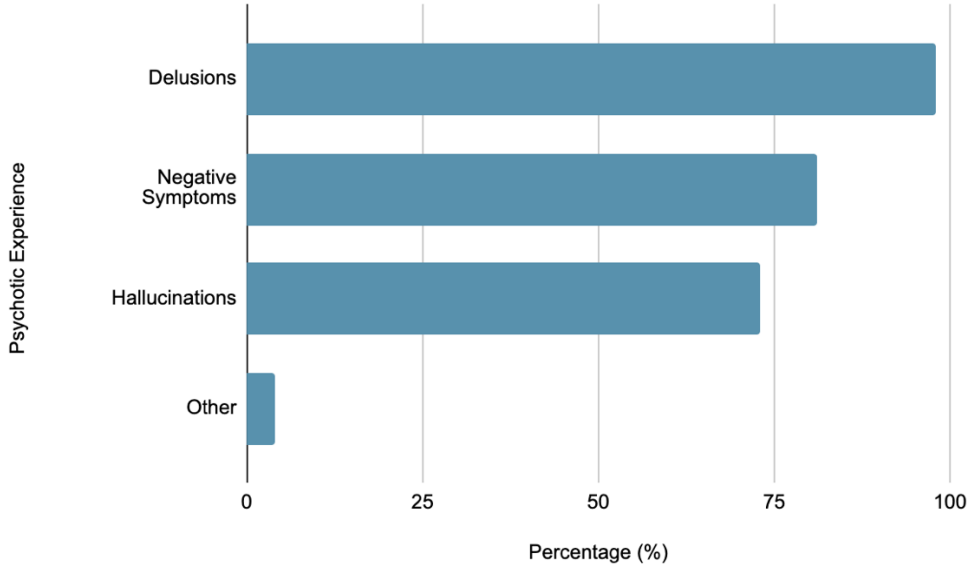
Participant Reports of Psychotic Diagnoses



The following figure illustrates psychotic experiences reported by participants in the survey. Many reported having two or more.

Figure 5.5

Participant Reports of Psychotic Experiences



In terms of religious/spiritual affiliation, 49% (n=49) of participants reported being religious and/or spiritual, 35% (n=35) reported not being religious/spiritual, and 16% (n=16) reported "other," usually identifying their specific tradition in the open response section. The age of participants ranged from 18 to 62, with the average age being 28.5.

5.4.2. Descriptive Statistics

Out of the 100 respondents, respondents reported using a variety of psychedelics (see Appendix B). Specifically, 43% (n=43) reported using psilocybin, 38% (n=38) reported using LSD, 6% (n=6) reported using ketamine, 9% (n=9) reported mixing a psychedelic with another psychedelic or MDMA, 2% (n=2) reported using DMT, 1% (n=1) reported using ayahuasca and

1% (n=1) reported using 2-BOH-CB, a phenethylamine in the 2-CB family, which generates experiences like psilocybin and LSD (Schulgin & Schulgin, 1991).

5.4.2.1. Personal Growth and Setting

60% (n=60) of individuals reported that their experience resulted in personal growth, 28% (n=28) of individuals reported that it somewhat resulted in personal growth, 9% (n=9) of individuals reported that it did not result in personal growth, and 3% (n=3) did not answer (see Appendix C). 86% (n=32) of those who used LSD reported some degree of personal growth, and 92% (n=38) of those who used psilocybin reported some degree of personal growth.

Out of the nine respondents who did not report personal growth, 33.33% (n=3) had used psilocybin, 55.56% (n=5) had used LSD, and 11.11% (n=1) had used MDMA. 100% (n=5) of those who reported no personal growth and using LSD reported not being fully comfortable in their setting (with four indicating 'somewhat comfortable' and one responding 'no'). The individual who used MDMA and reported no personal growth was uncomfortable in their setting. The two who used psilocybin and reported no growth reported being fully comfortable in their setting.

No reports indicated that use was conducted under supervision in the context of a clinical trial or with the presence of a therapist or clinician. A significantly large portion however directly described naturalistic or recreational use.

5.4.2.2. MEQ Scores

58 respondents completed all 11 items selected from the MEQ-30 that the research team chose to incorporate into the survey (see Appendix D). Individual total scores ranged from 1.45 to 10

(range: 0-10), with an average score of 7.1 (SD=2.00). Out of the 58 respondents, 49 (84.48%) scored higher than an average total score of 5, 20 (34.48%) scored higher than 8, and 9 (15.52%) scored higher than 9. 22 respondents who used LSD completed the mini-MEQ that was given, and the average (mean) score produced was 7.11 (SD=1.97). The average (mean) score was also 7.11 (SD=2.01) for the 24 respondents who reported psilocybin use. Cronbach's Alpha was calculated to determine the internal validity of this modified and condensed version of the MEQ and was found to demonstrate good and nearly excellent reliability with α=.087.

5.4.2.3. Reported Changes

Psychological, spiritual, emotional, and behavioral changes were captured by a range of items throughout the survey (see Appendix D). 67% of the respondents (n=67) reported experiencing deeper levels of spirituality or contemplation after their experience. 13% (n=13) did not report an increase, 17% (n=17) reported no change in their spirituality or contemplation levels, and 3% (n=3) did not provide an answer to this question.

51% of respondents (n=51) reported a better understanding of past events, memories, or traumatic experiences that played a significant role in their lives. In comparison, 29% (n=29) answered that they did not, and 19% (n=19) responded, "Somewhat."

Out of the 77 participants who completed the small 2-item subscale on feelings of love and appreciation following their psychedelic experience, the mean average score was 6.25 (range: 0-10; SD=3.02) with 64.94% scoring higher than a 5, 48.05% higher than a 7, and 20.78% a 10.

75 respondents answered the item asking them to rate how much their experience helped them feel more resilient towards life failures (0-10). 66 scored a five or higher, 53 scored a seven or higher, and 22 scored a 10. The mean average was 6.69 (SD=3.05).

5.4.3. Themes

Participants were asked, “Did your psychedelic experience result in personal growth?” and were allowed to select “Yes,” “No,” “Somewhat,” or choose not to answer. They were subsequently prompted to elaborate on their answer in 100 words or less. 97 participants answered the multiple-choice part of the question, and 75 of the 100 provided additional details in the qualitative follow-up. Two or more researchers independently coded the responses and found common themes among the sample, including (1) increased insight and perspective shift, (2) mystical, spiritual, and religious experiences, (3) improved mental and emotional well-being, (4) increased appreciation, (5) empathy and relationships, (6) better version and growth, (7) acceptance and self-love, and (8) adverse and mixed-type experiences. Saturation was determined to be reached based on theoretical reasoning and thematic induction analysis. This combinatory approach found consistent reporting of positive, mixed, and challenging experiences and more specific themes recurring in a predictable and pattern-like fashion.

Table 5.3

Qualitative Responses Describing Growth or Lack of Growth from Reported Psychedelic Experience

Theme	Description	Exemplar Quotes
Increased Insight and Perspective Shift	Psychedelic use led to increased understanding, insight, self-awareness, more objective thinking and viewing of the world, increased introspection, spawned realizations, learning life lessons, and/or shift in perspective	P10: *I saw myself as I really was* P42: *I realized how I want to be happy and how to let go of things that bother me* P65: *I felt I was able to see perspective on certain situations clearer…* P90: *[it] made me a lot more introspective in the long run*
Mystical, Spiritual, and Religious Experiences	The psychedelic experience resulted in becoming religious, seeing things as temporary, seeing everyone as one, a feeling of interconnectedness with the world, similar transcendent experiences, unable to explain in words and experiences of ineffability.	P33: *There is control beyond our understanding* P22: *[I] became religious…* P87: *I have changed since then, feeling more of a "one-ness" with all other living beings, more mindful of how my own thoughts affect me and how my actions affect others and myself* P55: *I've learned many valuable life lessons that I can't put into words*
Increased Mental and Emotional Wellbeing	Reports of symptomatic relief in domains such as rumination, overthinking, catastrophizing, suicidality, and hallucinations, increased joy/peace/calmness, and decreased fear of death	P20: *I felt I understood things more and I also chose not to kill myself (during the trip) so I chose life* P12*: I feel like my mind has started expanding a little bit, taking me out of rumination and constant loops and catastrophizing* P64: *It helped me realize that it's okay that fear and pain are a part of me. It let me connect with the traumatized part of myself and feel compassion for myself which I hadn't done before. It was one of the only times that crying felt liberating instead of shameful*

Increased Appreciation	Increased feeling of life, appreciation for life, increased appreciation for nature, mentioning increased possibilities in the world	P47: *...it made me really appreciate the life I have and being sober* P63: *It turned me away from pessimism and nihilism and materialism. And find value and beauty in all things, especially nature* P90: *...made me much more appreciative of nature*
Empathy and Relationships	Becoming more caring, wanting to help people, more consideration for others, understanding, focus on external relationships	P23: *I realized I had a deep far reaching empathy that I did not realize I had and I realized how I have been neglecting personal relationships* P52: *I felt more open to forgiving my husband…* P32: *Eventually it lead to me realizing I was the problem in my own relationship and changing who i was for the better*
Better Version and Growth	Individuals describe becoming better versions of themselves, feeling more like themself, mentioning specifically 'growth', and feeling compassion for myself	P6: *I think I was able to tap into and be a better version of myself. At least for the moment* P16: *I'm just a better person than I was 2 years ago* P19: *...I always grew a little bit from each [psychedelic] experience in some way*
Acceptance and Self-love	Acceptance of self, acceptance of one's reality, acceptance of the world, acceptance of things beyond control, loving oneself, and self-love	P53: *More self-acceptance and acceptance of my experiences.* P95: *I realized I had a lot of love in me, including for myself (I never tapped into the latter previously)* P44: *I think it helped me be more in the moment and accept whatever comes in life which has been very useful so far*

Negative and Mixed-type Experiences	Reports of negative experiences, terror, fear, symptom exacerbation, beliefs that use led to permanent damage, drug misuse/abuse, and various other adverse effects that are either reported alone, or alongside statements of positive growth and change	P24: *It has made me realize the patterns and problems in my life. I wouldn't be aware of them if I didn't take drugs. However, it also made me really too self-aware in a crazy level, made some of my symptoms stronger such as intrusive unwanted thoughts and guilt* P68: *It has made me completely dependent on someone else. Unable to trust reality and my mind to grasp what's true.* P78: *[I] gained [a] permanent trip, Lost suicidal ideation. Growth in some ways hindrance in others.*

5.4.3.1. Increased Insight and Perspective Shift

One major theme respondents described was increased insight, gaining newfound knowledge, and a shift in perspective that often led to improved self-awareness. Many statements such as these were observed in participants and included experiencing personal growth due to changes in their outlook or within themselves and the world around them, seeing themselves for who they truly were, and becoming more introspective.

5.4.3.2. Mystical, Spiritual, and Religious Experiences

Another significant theme was that respondents' psychedelic experiences featured mystical, spiritual, and religious elements. These responses involved testimonies describing a range of experiences, such as interconnectedness, unity, an increase in one's faith or religious beliefs, transcendence, enhanced sensory awareness, and ineffability. These and other similar statements are representatives of a theme that encapsulates a deepening of spirituality and faith in a greater power, mystical experiences such as being interconnected with other beings and the universe, feeling as if their psychedelic experience was indescribable, and more.

5.4.3.3. Improved Mental and Emotional Well-being

Another theme among participants was related to improvement in overall emotional and psychological health. This theme emphasized newfound insights about the importance of caring for oneself and one's emotional and mental health. Respondents frequently reported insight into their maladaptive coping mechanisms and how modifying such patterns can lead to a more

satisfied life. Several participants also reported feeling significantly less stress and anxiety after their experience, and several reported decreased suicidal ideation.

5.4.3.4. Increased Appreciation

Increased appreciation was another theme that occurred across the responses. These reports centered around appreciating and valuing the various aspects of life, feeling a newfound appreciation of life and/or nature, and recognizing the beauty of life. Participants describing these experiences also reported feeling grateful for personal relationships, having an increased sense of purpose, appreciating more experiences and opportunities, and acknowledging the positive aspects of life.

5.4.3.5. Empathy and Relationships

A less prominent but still widely reported theme was empathy and personal relationships. Several participants described realizing ways they were engaging in relationships, and how their psychedelic experience generated increased empathy, heightened emotional intelligence, and care for others. Some participants also described being to recognize faults in their relationships and ways to move forward.

5.4.3.6. Better Version and Growth

Another less common theme was the better version and growth of an individual, where testimonies from participants centered around personal development, self-improvement, and/or

feeling like oneself again. This theme was established from expressions of self-reflection, goals, aspirations, and taking steps toward bettering oneself.

5.4.3.7. Acceptance and Self Love

The final positive theme discovered was that of acceptance and self-love where participants expressed acceptance of oneself, reality, the world, and things beyond control, as well as compassion for oneself and self-love. Themes related to acceptance varied with some participants reporting acceptance of death, self-acceptance, and accepting their fear and pain. Some also described increased self-compassion.

5.4.3.8. Negative and Mixed-type Experiences

While most participants reported overall positive psychedelic experiences that resulted in personal growth, mystical-type experiences, and increased insight, several individuals reported that their experience—in part of in whole—was challenging, negative, and harmful. Some described experiences of terror and dysphoria, with two stating that their psychedelic experience catalyzed or caused their psychosis. Some reported that during their psychedelic experience, they believed they were dying, while others stated they thought they would never become sober again. Some also stated their belief that their psychedelic experience caused irreversible damage. Several also reported that their experience was positive but alluded to it not being particularly impactful or transformative.

Table 5.4

Exemplary Vignettes Demonstrating Typical Overall Positive Experiences Among Survey Respondents

ID	Psychotic Diagnoses	Psychotic Symptoms	Psychedelic Used	Drugs Mixed	Comfort in Setting	Experience Overall
37	Schizophrenia, Psychosis Not Otherwise Specified, Schizoaffective Disorder	HAL, DEL, NEG	LSD	No	Comfortable	*A large part of the meaning of this experience for me was based on my prior experiences with psychosis, which have been very intense and frightening periods of my life. I have long read so many statements/guidance about risk of use of psychedelics for those with a history of psychosis, and so I had been somewhat worried. But approaching this experience with LSD (carefully), and being able to move with it, and learn from it, was beautiful. I felt more whole following the experience, and it reminded me of how far I've come in my recovery*
75	BP with Psychotic Features	HAL, DEL, NEG	PSL	No	Somewhat comfortable	*It felt very freeing of mental baggage, grounding, and calming. Before taking it, my mind was all over the place and it felt full of traffic and blocked roads. Afterwards, I felt like my moods were very stable and that my brain's thinking has finally been organized into a functional state*
77	First Episode Psychosis	HAL, DEL, NEG	KTM	No	Comfortable	*I was totally dumbfounded. I expected to die but instead got my life back with the snip of a finger. And who the hell gets out of a psychosis on ketamine? [That was the] last thing in the universe I expected to happen*

Note. Psychotic symptoms were coded as hallucinations (HAL), delusions (DEL), and negative symptoms (NEG). Psilocybin is represented as PSL, and ketamine is represented as KTM. When respondents did not answer the question regarding whether they mixed drugs or alcohol with their psychedelic, we assumed it meant they did not. BP stands for bipolar disorder. For additional information refer to Appendices B and C.

Table 5.5

Exemplary Vignettes Demonstrating Typical Overall Mixed-type Experiences Among Survey Respondents

ID	Psychotic Diagnoses	Psychotic Symptoms	Psychedelic Used	Drugs Mixed	Comfort in Setting	Experience Overall
32	BP & MDD with Psychotic Features	HAL, DEL, NEG	LSD	Rx, Cannabis	Comfortable	*At first the most amazing thing I have ever done but eventually after abusing it one day it very quickly became my enemy when I learned all I needed to from it.*
367	BPD with Psychotic Features	HAL, DEL, NEG	LSD	Rx	Somewhat comfortable	*There were parts of it that were fantastic and amazing. There were parts of it that were brutal and painful. I hurt people who were already hurting. I hurt myself because I was hurting. It was a transformative process. It could have gone better, but I don't regret it.*
89	N/A	HAL, DEL, NEG	PSL	NCA, Cocaine	No	*It had some good moments but the latter part was very unpleasant, the months following were a confusing mess where my repressed problems were brutally exposed forcing me to deal with them, but when everything was over after about 4-6 months everything started to get much better and I feel my world view has improved and I've also learned a lot of things about myself which I rather wouldn't have initially but now feel very happy I did so overall I think in the end it turned out good.*

Note. BPD represents borderline personality disorder; MDD represents Major Depressive Disorder. NCA represents 'nicotine, caffeine or alcohol' and Rx means prescription psychiatric medication. Participant 89 did not state they were diagnosed with a psychotic condition. For additional information refer to Appendices B and C.

Table 5.6

Exemplary Vignettes Demonstrating Typical Overall Negative Experiences Among Survey Respondents

ID	Psychotic Diagnoses	Psychotic Symptoms	Psychedelic Used	Drugs Mixed	Comfort in Setting	Experience Overall
63	N/A	HAL, DEL, NEG	LSD	NCA, CAN, Rx	No	*Awful. Made the psychosis much much worse*
70	Schizo-affective Disorder	HAL, DEL, NEG	LSD	Rx	Somewhat comfortable	*This was one giant, 15-hour bad trip. I've done psychedelics multiple times and always became completely delusional and hysterical. I stay away from them now.*
75	N/A	HAL, DEL	PSL	No	Comfortable	*Regrettable. I have never been the same. Since then, I constantly feel stuck in trauma reactions. I now have autoimmune disorders and chronic pain from the experience*

Note. For additional information refer to Appendices B and C.

5.4.4. Vignettes

These vignettes were selected because they showcased overall positive, negative, or mixed-type experiences representative of the sample. They also highlighted factors that could contribute to the experienced outcomes, such as whether the psychedelic was mixed with other drugs, and the participant's comfort level in their setting. The quotes centered in these vignettes were qualitative responses at the end of the survey, where participants were asked to describe their overall experience and a thematic content analysis technique. The technique, which was used to determine whether responses were coded as overall positive, negative, or mixed, sought to interpret subjective phenomenological reporting as having a therapeutic, adverse/negative, and or mixed effect, which coincided with the specific 'type' classification. The classification system utilized specific criteria to determine coding, namely the inclusion of explicit language describing positive experiences such as insight, and growth, and negative experiences like exacerbation of symptoms or terror. Criteria for identifying those whose experiences were coded as 'mixed-type' described combinations of these experiences (e.g., it was beautiful and painful at the same time). High agreement was found. However, there was one instance of a mixed-type experience being initially coded as negative, but agreement was met after a discussion among the research team and this was changed.

Table 5.4 depicts individuals' most common responses, which were overall positive experiences. In the table, participants 37, 75, and 77 all describe how their psychedelic experience was positively impactful, helped them to stabilize and become functional, and shifted their perspective for the better. Table 5.5 illustrates another category of having positive and negative effects alongside each other, i.e., mixed experiences. Respondents who reported mixed effects often describe euphoric and dysphoric moments co-occurring at different times

throughout their experience. At the same time, a less common theme that was nonetheless still present was table 5.6, where individuals describe overall negative experiences, such as dysphoria and experiencing adverse effects like symptom exacerbation or mental health crises.

Of note, none of the individuals in the above vignettes who reported overall positive experiences combined their psychedelic drug with another drug, while most who had mixed experiences, and overall negative/adverse experiences did. In addition, most who had mixed, and adverse experiences did not report being fully comfortable in their environment, whereas individuals who had overall positive experiences did report a fully comfortable setting. Another potentially important observation is that most who reported mixed and negative experiences in the tables above used LSD.

5.4.5. Case Studies

Case studies provide an in-depth examination of psychedelic experiences in the sample and provide a more holistic understanding of participant backgrounds and experiences overall. Three exemplar cases were selected to demonstrate the range of experiences individuals have reported rather than the most common experiences. The first case study demonstrates an overall positive experience, the second portrays an experience with both positive and negative elements, and the third case study conveys overwhelmingly adverse and negative effects. The overall type of experience was coded using inductive thematic content analysis, as described above. Pseudonyms are used to protect participants' identities.

Table 5.7

Case Study Characteristics and Demographics

	Case Study 1 **Jason**	Case Study 2 **Ahmed**	Case Study 3 **Angelika**
ID #	81	74	20
Age	27	23	20
Race	White	Mixed (Black, White)	White
Gender	Male	Male	Transgender
Country	USA	United Kingdom	USA
Diagnoses	Schizophrenia	Psychotic Disorder, Not Otherwise Specified	Schizoaffective Personality Disorder, C-PTSD, Anxiety, Depression, OCD
Symptoms	HAL, DEL, NEG	HAL, DEL, NEG	HAL, DEL, NEG
Drugs Used	Psilocybin, SSRIs, antipsychotics, anti-anxiety medications	LSD, Alcohol	Psilocybin

Personal Growth	Somewhat	No change	Somewhat
Spirituality/ Contemplation	No change	Increased	Increased
Overall	Positive	Mixed	Negative

Note. For additional data on participants refer to Appendices B and C.

5.4.5.1. Case Study #1

Jason (Participant ID No. 81) is a 27-year-old White gay man from the U.S. with a reported diagnosis of schizophrenia and a familial history of psychotic disorders. In his own words, his chief complaints are that he frequently experiences hallucinations, typically multiple times daily, and has persecutory delusions and used to have grandiose delusions as well. He reports suffering from "polydipsia, disorganized thoughts/speech, rumination, anhedonia, avolition, social withdrawal, and other negative symptoms." He also reports that "a lot of his negative symptoms began when [he] was young, probably around nine, and that the positive symptoms began when [he] was 20." Jason states that he has used multiple psychedelic substances throughout his lifetime, including psilocybin, LSD, peyote, and MDMA. For the survey, he elaborated on an experience with magic mushrooms six years ago, which he remembers well. He does not explicitly state the dose; however, he reports that generally when he used psilocybin, he used over 4 grams each time.

During this experience, Jason reports having taken SSRIs, antipsychotics, and anti-anxiety medications within three days prior to his psychedelic experience. He reports being in a 'serene' mood prior to the experience and that this was a time in his life after his positive symptoms had developed and "were under control." He reports that he was somewhat comfortable in his environment, at the home where he and his ex-partner lived. He states he took

the mushrooms with his ex-partner and a friend, expecting them to help provide a euphoric experience and help relieve stress. During the experience, he "felt relaxed for once," which he described as "very rare." He states that his mood was "elevated positively" and that he could remember what "seemed to be repressed memories." Jason also states that his experience resulted in personal growth somewhat as it put him "at ease to remember some repressed memories in a non-traumatic way."

He reports that his level of spirituality remained the same after the experience, that he felt somewhat more connected to the Earth and the life on it, felt "more connected to people because of a lack of paranoid thinking," said that he was able to establish a better understanding of past events, memories, and traumatic experiences that played a significant role in his life, and that he was "able to look at what other people could more realistically be reacting to instead of through my paranoid thoughts." He states that he did not experience physical side effects after the experience and rated the 5 of 9 items he responded to on the MEQ items in the survey as "10." He stated in his closing response that "[the experience] reduced paranoia and caused some euphoria. It was easier to look at the world around [him] without the burden of paranoia."

5.4.5.2. Case Study #2

Ahmed (Participant ID No. 74) is a 23-year-old biracial (Black and White) heterosexual male from the United Kingdom. He reports being diagnosed with "Psychotic Disorder, Not Otherwise Specified" and has a history of hallucinations, delusions, and negative symptoms. Ahmed also indicated a history of psychotic disorders in his family. Ahmed's chief complaints involve mostly negative symptoms, including withdrawal, loss of enjoyment, mental acuity, decreased attention span, and ability to apply effort.

For the survey, he describes a moment when he used 400ug of LSD earlier this year, during which he also used alcohol. His experience lasted over 12 hours, and he reports swallowing/ingesting the LSD. He reports not taking other substances and/or prescription medication when under the effects of the drug. He immediately describes his mood before taking the LSD as “interested/curious, happy, joyful/giddy, and grateful.” He reports that he was at the pub when someone sat at his table and asked if he wanted some LSD. He reports that he said yes, but was unsure; however, he was excited to try it. He describes being somewhat comfortable in his setting, alone in his house at 3 am, and worried about “offsite staff swinging by,” apparently because of the nature of his work. He reports that his expectation regarding the experience was “to get really fuc**d up.” During the experience he felt “excited, happy, curious and anxious at times" and upon becoming sober, described his experience as “fun.”

He did not feel the experience resulted in personal growth and said that in the following days, he performed poorly at work and was pulled over under suspicion of intoxication. He states having increased levels of spirituality and contemplation after the experience, feeling increased happiness “for a short while” and describes that experience as a “...nice time.” He also rated seven items on the MEQ with scores of 8 and higher. However, Ahmed also reports that the experience “really fucked up [his] vision and caused disordered sporadic thinking”; it also “severely impaired [his] thinking ability.” He reports that during the experience, it “flipped by the moment from entertaining to anxiety-provoking but not so much that [he] was bothered” and that “towards the end of [the experience], the novelty wore off and [he] could not wait to be sober.”

5.4.5.3. Case Study #3

Angelika (Participant ID No. 20) is a 20-year-old bisexual White agnostic transgender person from the U.S. who reports a diagnosis of schizoaffective personality disorder, complex PTSD, anxiety, depression, and OCD. They report psychotic experiences, including hallucinations, delusions, and negative symptoms. Their chief complaints involve having highly impaired functioning, reporting not knowing if they will ever be able to live independently, having "scary delusions," inability to differentiate what is real from what is not, difficulties regarding relationships, and PTSD symptoms. They report having their first psychotic episode when they were 13 and then having more symptoms when they turned 18, being diagnosed with major depressive disorder and social phobia when they were 15, having their first manic episode at 18, and being hospitalized and given medication for the first time during this experience. They describe having minor symptoms currently.

For the survey, Angelika describes taking a medium dose of psilocybin mushrooms at 17 and not being in an actively psychotic episode. They report trying psilocybin to help manage mental health symptoms and for recreational purposes. The experience lasted 3-6 hours, and they reported that they were not under the influence of any psychoactive substances prior to dosing. They report not feeling comfortable and safe in their setting, stating that they were with a friend in downtown Chicago which was "a strange place…" that "...[they] never traveled…" and that it was "...big and crowded." They reported expecting to see visuals, feel happy, and have fun during their experience, but instead felt lost, depressed, and towards the end, suicidal. They report that their experience resulted in personal growth somewhat, stating that they felt they "understood things more" and "also chose to not kill [themself] during the trip and choosing life." They also report understanding the world and society more, realizing the interdependence of natural phenomena more, and at the same time, seeing everything as more straightforward.

They also gained insight regarding death, saying it was natural and "not that big of a deal." They describe understanding life more after their experience but also have a dark and depressing worldview, which they now disagree with. They also report that during the experience, they felt people were cruel and life was unfair, but at the same time felt closer to the friend they had taken the psilocybin with.

They scored an average of 4.5 on the MEQ items in the survey and rated both items regarding increased love and appreciation following the experience as 0 but stated that the experience did increase their levels of contemplation and spirituality. They mention that while "it was kind of fun at first," the experience "got dark fast" as they "got lost in Chicago, saw the world as evil and unfair" and contemplated suicide at the time.

5.5. Discussion

Recently some scholarly literature has been published regarding psychedelic experiences and individuals with psychotic disorders (Arnovitz et al., 2022; DellaCrosse et al., 2022; Friesen, 2022; Mahmood et al., 2022; Morton et al., 2022; Wolf et al., 2023; Ye et al., 2019; Zeifman & Wagner, 2020). However, research has mostly been theoretical and fail to utilize a participatory approach by asking individuals with lived psychotic experiences about their experiences with psychedelics. The purpose of this study was to understand how individuals with psychosis and psychotic disorders experience psychedelic drugs with the understanding that inclusion and exclusion of groups in psychedelic clinical research must be regularly revisited and reassessed. Granted that the topic of psychedelics and individuals with psychosis has long been considered taboo, we believe that the empirical data captured by this cross-sectional retrospective survey helps to clarify that this group can experience benefits from psychedelics. Such data can also be

applied to the psychedelic world by helping to shed light on how much weight diagnosis should be given when assessing PAP candidacy.

Furthermore, it is interesting and important to observe that many participants of the survey described using psychedelics in a naturalistic setting. Indeed, none mentioning use in the context of a clinical trial or under professional supervision, which may suggest that all participant experiences may have been recreational in nature. It is noteworthy that some even described their experiences as being somewhat impromptu, which is interesting considering that many individuals are apprehensive about of using psychedelics in this way.

Another point that is worth mentioning is that only a small portion of individuals—approximately 11 individuals—reported overall negative experiences. This may point to an over-determination or positive bias among the participants of the study as the phenomenon of psychedelic-induced psychosis is a common concern and a popularly discussed topic within psychedelic circles. The lack of these accounts may be explained by the fact that individuals who experience psychedelic-induced psychosis are not stable enough to complete a survey about their experience or are unwilling to discuss their experience due to the discomfort involved in revisiting the experience, even if only temporarily. However, another explanation could be that there is indeed a small portion of individuals who experience psychedelic-induced psychosis and that instances of this phenomenon are overestimated.

Overall, psychedelic clinical trials continue to exclude individuals with personal or familial histories of psychotic experiences and disorders, despite a lack of evidence demonstrating that psychedelic treatment may not be beneficial to this group. A cross-sectional survey was designed to ask individuals with psychosis and psychotic disorders about their psychedelic use to determine if there may be reason to implement or avoid psychedelic care and

research in this group. Results indicate that individuals with psychotic experiences and conditions use various psychedelic drugs naturalistically with varied outcomes and most of the sample reported that their psychedelic experience resulted in some personal growth. Many also report mystical-type experiences, increased insight, improved mood, appreciation for life, and symptomatic relief. Although a small portion reported negative experiences. Interestingly, an initial analysis shows that negative experiences seem to be associated with concomitant drug use and use in unfamiliar or uncomfortable settings.

5.5.1. Statistical Observations

The study collected data from a total of 100 participants with psychotic experiences and/or disorders, demonstrating that psychedelic drugs are used by this population. Of the 100, 43% (n=43) reported using psilocybin mushrooms, 38% (n=38) reported using LSD, 9% (n=9) reported mixing a psychedelic with another psychedelic or MDMA, 6% (n=6) reported using ketamine, 2% (n=2) reported using DMT, 1% (n=1) reported using ayahuasca, and 1% (n=1) reported using 2-BOH-CB (see Appendix B).

Regarding personal growth, minimal variation was observed across drug categories with 86% (n=32) of those who used LSD reporting some degree of personal growth resulting from their experience compared to 92% (n=38) of those who used psilocybin mushrooms. Of the 9 who reported no growth from their experience, 5 reported using LSD, 3 reported using psilocybin mushrooms, and one reported MDMA, suggesting that LSD could be associated with more negative experiences in this population, however more research must be carried out to make this determination.

Average scores from the condensed Mystical Experiences Questionnaire (MEQ) demonstrated that moderately intense mystical-type experiences were relatively common, with an average total score of 7.1 (SD=2.00) among the 58 who completed all items. Furthermore, 70% (n=70) of participants reported that their psychedelic experience helped them to process traumatic events and memories while 67% (n=67) reported a deepening of spirituality or contemplation following their experience. More than 60% also indicated that their experience resulted in increased feelings of love and appreciation, and improved resilience against life challenges. As the sample was too small and lacked sufficient variability, more research with larger samples should be carried out to allow for more robust statistical testing using correlational analyses, and multiple regressions.

5.5.2. Thematic Analysis

Thematic analysis indicates that the sample primarily experienced positive experiences, which featured moments of insight, increased awareness, spiritual and mystical experiences, improved mood, heightened empathy, disruption of maladaptive behaviors, appreciation of life, personal growth, self-love and appreciation, and improved relationships. At the same time, several individuals reported experiencing euphoria and insight accompanied by distressing moments, which were described as adverse and mixed effects, replicating findings from Morton and colleagues (2022). These trends suggest that psychedelic experiences reported by this sample may occur along a spectrum and continuum and are suggestive of the non-binary nature of such experiences. More research must be done to determine to whether this population experiences negative and mixed experiences at a greater rate or frequency compared to other diagnostic groups, as well as if negative effects and consequences are more severe.

5.5.3. Case Studies and Vignettes

Results from the case studies and vignettes further confirm the presence of three kinds of psychedelic experiences, i.e., those that are overall positive, negative, and mixed. They showcase that while most reports are overwhelmingly positive, some are mixed, and some are negative, suggesting that binary models of psychedelic experiences (i.e., positive versus negative) are insufficient. For example, Angelika described adverse effects like psychedelic-induced suicidal ideation, however, also stated that the experience deepened their levels of contemplation and spirituality while also increasing their understanding of life. Similarly, vignettes also depict this trend such as participant 67 who described their overall experience as having parts that were "fantastic and amazing" and "brutal and painful." This suggests that psychedelic experiences may be best defined as continuum-like, multifaceted experiences.

When looking at the selected vignettes and case studies it is difficult to discern whether mixing other substances with psychedelics yields positive, mixed, or negative results overall as sufficient variability was observed across multiple respondents who reported mixing drugs at the time of their reported psychedelic use. However, it may be relevant to note that most individuals who had negative and challenging experiences combined LSD with another substance and/or used LSD in an uncomfortable or somewhat uncomfortable setting. Meanwhile, data point out that more individuals who consumed psilocybin or LSD in a comfortable setting resulted in personal growth compared to those who were in uncomfortable and somewhat comfortable settings. Larger samples however must be collected to carry out statistical tests such as correlations and multiple regressions. Such tests could also investigate the effects of combinatory drug use, if the sample if large and diverse enough.

5.6. Study Limitations

The study has several limitations. For one, the study is somewhat limited in terms of diversity, given that ethnoracial diversity is limited and that significantly more individuals describe positive symptoms of psychosis than negative symptoms. This may limit the generalizability of the findings. In addition, it is worth noting that the sample may not represent the broader population, given that those who took the time to respond to the survey may feel more strongly that their psychedelic experience was transformative, in either a positive or negative way, potentially biasing the results. Additionally, some participants combined their psychedelics with other drugs ranging from alcohol and caffeine to benzodiazepines and cannabis, which may have also affected reported experiences in a range of ways.

In addition, it is worth noting that participants may not have fully understood various items, and/or did not respond to the survey accurately or truthfully. This is evidenced by some individuals being inconsistent in their reporting, such as Ahmed (Participant No. 74) in Case Study #2 who had high MEQ scores but described their experience as "fun." At the same time, one possible explanation for this finding is that for individuals who regularly experience perceptual distortions such as Ahmed, psychedelic experiences may seem rather ordinary. Similar evidence suggesting a lack of consideration when completing the survey includes individuals who report high MEQ scores but who mention that their spirituality remained unchanged such as Jason (Participant No. 21) in Case Study #1. One possible explanation however is that Jason was highly spiritual prior to the experience he describes in his report, perhaps due to a previous experience with psychedelics or otherwise. Indeed, this would not be unheard of considering that many people who are attracted to psychedelics are drawn to them

exactly because of their interests in spirituality and personal development. However, these explanations for both Ahmed's and Jason's responses are speculative as the survey did not provide an opportunity for follow-up.

Another important limitation that must be acknowledged is that many survey respondents recounted experiences that occurred one or more years ago, with some being as many as six years ago such as with Jason (Participant No. 21). However, while such extended periods of time elapsing may distort memories significantly, it is also worth considering that psychedelic experiences can be extremely important life events comparable to the birth of children (Griffiths et al., 2006). Given the magnitude and significance of these experiences, it is possible that participants may have been able to recall them more accurately compared to a mundane event from so long ago. However, this reasoning is speculative, and it remains highly probable that experience-far accounts are less accurate than reports of recent experiences such as those that occurred within the past year or last six months.

Other limitations include a lack of consistent specification on part of the survey as to whether psychotic symptoms or disorders reported occurred prior to or after reported psychedelic use. In addition, prevalence of substance use disorder and symptomatology in the sample is unknown.

5.7. Future Research

More research must be conducted to determine if this population is more likely to have one specific type of psychedelic experience (positive, mixed, or negative) and how these frequencies and degree of severity compare to other diagnostic groups. Additionally, more extensive studies that gather data from hundreds or more participants may adequately detect statistically

significant findings with tests such as whether individuals with specific psychotic-type symptoms or disorders are more likely to have mystical-type experiences or experience personal growth than other groups. Correlational analyses with large samples could also reveal whether different drugs and comfortability in setting are correlated to specific experiences and overall quality of experience. After sufficient preclinical research has been conducted, an initial clinical trial administering psychedelic-assisted therapy under clinical supervision for a small pool of individuals with histories of psychotic experiences may be appropriate.

5.8. Conclusion

Analyses suggest that the sample describes three types of experiences overall: positive, mixed, and negative, which replicates similar previous findings among a sample of individuals with bipolar disorder describing their experiences with psilocin-containing mushrooms (Morton et al., 2023). Consequently, psychedelic experiences are best described as multidimensional or spectrum-like. Most of the sample reported some degree of personal growth, experiences of insight, and mystical-type experiences with varying ranges of intensity, while a small proportion of the sample report negative experiences and adverse effects such as worsening symptoms. However, it is unclear precisely what may lead to such events as confounding variables such as comfortability in setting and concomitant use of substances obfuscate results. In addition, adverse effects commonly occur alongside positive effects, which may indicate a more extensive, generalizable trend for other groups, including healthy normals and those with anxiety, depression, and other conditions.

Another important finding is that the type of psychedelic experience one has may not be causally related to whether the individual reports the experience as resulting in personal growth.

Data also indicate the trend that comfortability and feeling safe in one's environment may be a strong, albeit imperfect, predictor in determining treatment outcomes, and that concomitant drug use may also play an important role in outcomes. Overall, the preclinical data in this study suggest that excluding this group from psychedelic clinical research may be erroneous as many report positive and therapeutic experiences.

Furthermore, given the abundance of positive survey reports regarding naturalistic psychedelic use, it is possible that supervised clinical use of psychedelics in tandem with psychotherapy could be an effective modality for treating both psychotic symptoms and comorbid symptoms of other problems like anxiety, depression, and substance use disorder for this population. PAP may also potentially be useful in treating schizophrenia and other more chronic psychoses. This is especially true given that negative and adverse experiences occurred when individuals used psychedelics in environments that have been demonstrated to problematic for psychedelic use such as outside of a supervised, familiar, and safe setting. Nevertheless, more research with larger samples must be carried out to conduct statistically significant analyses to make further determinations regarding the possible efficacy and safety of PAP for this group, as well as make suggestions for tailored PAP protocols.

CHAPTER 6: GENERAL DISCUSSION

6.1. Summary

Historically, psychedelic clinical research has excluded individuals with histories of psychotic experiences and psychotic conditions and to date no modern clinical trials examining potential benefits and risks of psychedelic-assisted psychotherapy for individuals with psychotic experiences and disorders have been conducted despite the fact that psychedelic use is not associated with the onset of mental illness (Friesen, 2022; Johansen & Krebs, 2018; La Torre et al., in press; Tupper et al., 2015). While inclusion and exclusion criteria are necessary for clinical research, and there are cases of individuals with psychosis becoming destabilized after using psychedelics recreationally, this does not justify the systematic exclusion of this group from psychedelic-assisted psychotherapy clinical trials. Indeed, naturalistic use of psychedelics often involves use in inappropriate and unsafe settings, impromptu use, and concomitant drug use, whereas clinically supervised PAP mitigates risk by maximizing safety. Thus, it is possible that PAP could be tolerated among this group. This is particularly evident after a review of the findings from the studies presented in this thesis.

To this end, there is reason to speculate that biases have determined what areas ought to be researched in the psychedelic space, and which topics may be best avoided. Psychedelics have a complex and intricate past in the United States, intertwined with stigma and bias (Davis et al., 2022; Friesen, 2022; La Torre et al., in press). This is also the case for individuals with histories of psychotic experiences and conditions, alongside Black and Indigenous communities, who are disproportionately labeled ‘mentally ill’ and overdiagnosed with disorders like schizophrenia and bipolar disorder (Akinhanmi et al., 2018; Faber et al., 2023; Muroff et al., 2008). It is important to acknowledge that during the first wave of psychedelic research, researchers inflicted

unspeakable harms to these groups (see Appendix A). As such, it is not surprising that many articles from this time describe extremely adverse reactions to high doses of psychedelics administered in the context of disturbing experimentation. It was also during this period that the Central Intelligence Agency (CIA) attempted to use psychedelics as instruments of psychological warfare and in so doing, also participated in inhumane experiments by funding studies that committed human rights abuses, particularly against BIPOC and institutionalized persons (Strauss et al., 2022). During this period, researchers erroneously believed that psychedelic and psychotic states of consciousness were one in the same, perpetuating misperceptions about the mechanisms of both psychedelics and psychosis (Friesen 2022). President Nixon solidified these notions with his War on Drugs, which utilized propaganda and scare tactics to lead individuals to believe that such drugs had no medical benefit and were instead likely to cause madness and insanity (Hall, 2022). At the same time, it is interesting to note that some studies also describe individuals with psychotic or 'psychoneurotic' conditions like schizophrenia benefitting from LSD and mescaline.

6.2. Findings, Implications, and Limitations

Findings from these two studies suggest that individuals with histories of psychotic experiences and psychotic disorders may be able to utilize PAP to treat their psychotic symptoms and/or their co-morbid problems like anxiety, depression, and substance use. Outcomes from the survey study demonstrate that in a cohort of 100 individuals with psychotic symptoms and disorders, the majority (88%) report personal growth from their psychedelic experiences while a fraction (11%) describe negative experiences and adverse reactions. Many also report mixed-type experiences or positive effects occuring alongside challenging moments.

None describe their psychedelic use in the context of a clinical trial or under professional supervision. Rather, most reports mention use in naturalistic or recreational contexts, which are generally without professional or experienced supervision, and lack appropriate support prior to, during, and following the dosing experience. Thus, it is interesting and significant to note that in this sample of individuals with psychotic symptoms and disorders, positive reports and reports of personal growth occur at such a high rate in naturalistic settings, given the caution that is exercised in contemporary research, which administers psychedelics only under careful clinical supervision.

Indeed, one implication of these results is that this group may engage with PAP safely to address their psychotic symptoms and/or co-morbid issues. Members of this group may receive great benefits from PAP, and this modality have a favorable safety profile as well. Overall, the high prevalence of personal growth and overall positive experiences alongside the relatively infrequent occurrence of negative reactions leads to an interesting consideration. Namely that if the rate of positive outcomes is so high in naturalistic settings, it would not be unreasonable to speculate that PAP's efficacy rate could be significantly higher. While it is worth noting that some individuals experienced negative outcomes, it is important to note that these events could be mitigated by employing harm reduction strategies and adequate clinical resources such as the accompaniment of a skilled therapist during dosing. Additionally, the preparatory phase of PAP could contribute to a reduction of adverse incidents by ensuring individuals have appropriate expectations, have sufficiently adjusted their set and settings, and consumed an appropriate dose. Integration sessions could also be beneficial by helping individuals make sense of their experiences, and monitor patients while being prepared to apply interventions—pharmacological or otherwise—if an individual experiences exacerbation of symptoms after dosing. At the same

time, while the incidence of negative outcomes is relatively rare in this population, it is important to note the severity of these incidents, which include suicidal ideation, symptom exacerbation, and more.

Findings from the first study echo those found in the second. Specifically, clinicians with expertise in PAP, psychiatry, medicine, and psychotic disorders explained that PAP is not necessarily contraindicated for everyone with personal or familial histories of psychotic experiences. At the same time, exclusion criteria do not exist in a vacuum, and rather are required for clinical research by the FDA and other health organizations such as Health Canada. The overarching consensus of the expert participants interviewed was that PAP could be safely administered to some individuals in this group for the treatment of their co-occurring problems like anxiety and depression, or perhaps also for psychotic symptoms, particularly those which may be in large manifested because of traumatization. Some also alluded to the fact that we will have to eventually conduct studies that explores the possible efficacy of PAP for all kinds of groups, including those with more chronic forms of psychosis such as schizophrenia. At the same time, experts strongly suggested that PAP protocols for this group must include high levels of support, particularly in the initial phases of research, and that it would be important for participants to be capable of building strong rapport with their therapist as results from the first study emphasize the importance on the strength of the therapeutic alliance in the context of PAP.

6.3. Precautions and Potential Contraindications

Still, caution is warranted as it is still unknown whether this subgroup is at a heightened risk of experiencing adverse effects or negative experience, and whether adverse reactions are more severe compared to other diagnostic groups. A range of contraindications may also exist for this

group, including the presence of psychotic diagnoses that etiologically caused by seizure conditions, substance use disorders, or spiritual emergency. Presence of some psychotic symptoms may also individuals make less amenable to PAP such as psychotic mania, which could be exacerbated by the heightened euphoria or revelatory insights psychedelic experiences can produce. The presence of paranoid thinking may also affect one's ability to respond positively to PAP by preventing individuals from forming trust with their therapist of being vulnerable. Other considerations include acknowledging that chronic use of compounds that are commonly associated with drug-induced psychosis such as amphetamines like MDMA may be best avoided (Curran et al., 2018; Hasan et al., 2020; Henning et al., 2019; La Torre et al., in press; Paparelli et al., 2011). Considering the dopamine hypothesis of psychosis and schizophrenia, caution should also be extended to the use of any compounds that increase dopamine levels such as psilocybin-containing mushrooms and other psychedelics that contain phenylethylamines, and high-dose LSD (Meltzer & Stahl, 1976). This precaution may also suggest excluding individuals who have experienced any form of drug-induced psychosis in the past, including cannabis-induced psychosis acknowledging the potential risks associated with cannabis use for this population.

Other considerations include if the individual interested in receiving PAP has supports outside of psychotherapy and clinical care (La Torre et al., in press). While one possible model involves individuals with psychosis receiving inpatient care following their dosing session, ultimately patients should ideally have adequate social networks upon termination in order to be monitored and prevent relapse. Being able to receive partake in integration after dosing and participate in ongoing psychotherapy would also be an important consideration and inability to do so may also be a contraindication (Bathje et al., 2022). Another risk involves the possible

onset of hallucinogenic persisting perception disorder (HPPD), which has been reported by some following PAP (Halpern et al., 2018; Lerner et al., 2014).

6.4. Conclusion and Future Directions

In conclusion, these studies shed light on how individuals with histories of psychotic experiences and psychotic diagnoses, which are psychopathological in nature, experience psychedelics, and how this group may experience PAP either for addressing psychotic symptoms, and/or other issues. As demonstrated, the historical exclusion of this group has hindered scientific progress and prevented advancement.

The expert opinions from this study acknowledge that PAP could be a viable treatment option for some individuals in this population under certain circumstances, such as having adequate support in place, and possessing qualities that could allow the individual to form a therapeutic alliance with their provider. Experts also point out that individuals whose psychotic symptoms may be linked to trauma may benefit from trauma-informed psychedelic modalities such as MDMA-assisted treatment.

The data collected from the large online phenomenological survey provides similar insights into how individuals in this population may experience PAP, suggesting that it may indeed be an effective treatment option given the high prevalence of positive experiences in naturalistic settings. However, caution is strongly advised as this study was among the first of its kind and more research must be carried out to determine if these expert recommendations are sound and whether the survey findings are representative of the broader population.

Several limitations to these studies exist as outlined above in their respective sections, and it is important to acknowledge how these may affect conclusions drawn from the studies'

corresponding datasets. Major limitations include the survey being retrospective and relying on participants to recall experience-far accounts, sometimes as much as six years ago. In addition, there may be bias regarding who responded to the survey as individuals who did experience negative consequences from psychedelic use may not wish to discuss painful memories via an anonymous online survey. It is also possible that individuals who experienced functional impairment because of psychedelic use are not healthy enough to respond to such requests. Additionally, sampling of experts was not entirely random.

Areas for future research include carrying out an initial clinical trial with individuals in this population to assess safety and efficacy of PAP. This research should utilize specially designed protocols that incorporate what has been outlined in these studies, such as ensuring appropriate support systems are in place, qualities of the ideal candidate, possible advantages, and disadvantages of certain psychedelic drugs over others, and ability to provide emergency medical care if needed. Other important avenues for future research include conducting participatory research at all levels of studies, asking people with lived experiences of psychosis and psychotic disorders to collaborate on research design, hypothesis development, data collection and requirement, and interpretation of findings. Involvement should also center this group's direct experiences with psychedelics, whether they would be interested in exploring PAP, why this treatment option might be effective, and whether it might harbor some risks. Another possibility includes using the survey used in the second study of this thesis to collect data from thousands of participants to allow for robust statistical testing and exploring correlations between kinds of experiences and specific symptom endorsement, diagnosis, drug use, set and setting, and other variables of interest.

Overall, the findings in these studies highlight that while some PAP protocols may be inappropriate for individuals with psychotic experiences and disorders, this does not warrant exclusion from all psychedelic research. As experts and individuals with lived experience have articulated, members of this group can and do report having profoundly impactful, mystical psychedelic experiences that often lead to personal growth and in some cases lead to mental health improvement. At the same time, it is important to note that approximately 11% did report overall negative experiences, and experts strongly recommended exercising caution.

By continuing to research this topic, we can strive for evidence-based recommendations regarding PAP and potentially expand the therapeutic possibilities of this new and exciting modality of healing. Most important of all, as we explore this breakthrough frontier in medicine and healthcare, it is imperative to adopt ethically sound practices and ensure inclusivity and equity, so that everyone may receive a fair and equal chance of feeling better, regardless of race, skin color, cultural heritage, gender, sexual orientation, disability, religion, mental health disorder, or any other aspect of their personhood.

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Appendix A

References for Studies on Individuals with Psychotic Symptoms and Disorders from the First Wave of Psychedelic Research

Reference	Substance	Population Type	Observed Symptomatology	Results
Guttmann, E. (1936). Artificial Psychoses Produced by Mescaline. *Journal of Mental Science*, *82*(338), 203–221.	Mescaline 0.1 - 0.4 g.	60 “normal persons” (Medical students Undergraduate students 3 psychopathic patients Etc)	**Physiological** Rapid pulse Mydriasis Nausea Salivation Sweating or dryness Anaphrodisiac **Psychological** Euphoria Hallucinations Anxiety Impaired reasoning and perception	Short-term introspective thinking Short-term fatigue
Hoch, P.H., Cattell, J.P., & Pennes, H.H., (1952). Effects of mescaline and lysergic acid (dLSD-25). *American Journal of Psychiatry*, 08, 579-584. https://doi.org/10.1176/ajp.108.8.579.	Mescaline 0.4 - 0.6 grams LSD 10 - 120 µg	59 schizophrenic patients (mescaline) 24 males 39 females 21 schizophrenic patients (LSD)	**Physiological** *Mescaline* Hostility Sexual tendencies *LSD* Headache Trembling Nausea Relaxation **Psychological** *Mescaline & LSD* Anxiety increase Depression Paranoia Hallucinations Somatic disturbances Euphoria *LSD* Emotional disturbances Relaxation Depressed with retardation Anxiety	Short-term aggravated mental symptomatology in people with schizophrenia Some patients with obsessive-phobic tendencies had symptom disappearance under the influence of mescaline

Liddell, D. W., & Weil-Malherbe, H. (1953). The effects of Methedrine and of Lysergic Acid Diethylamide on mental processes and on the blood adrenaline level. *Journal of neurology, neurosurgery, and psychiatry,* 16(1), 7.	LSD 40 - 60 µg. Methedrine 40 - 60 mg.	10 LSD Patient Cases 11 Methedrine Patient Cases Age: 22-61 yr. Various Mental Disorders with ≈ Equal sex ratio.	**Physiological** Adrenaline increase Blood sugar increase Increased Tension Abreaction **Psychological** Mood swings (LSD) Hallucinations (Methedrine) Euphoria Movement and speech delay; unworthiness (Depressed patients) Catalepsy and catatonia (Schizophrenic patients)	No long term negative symptoms recorded. Short-term insomnia (methedrine)
Pennes, H.H. (1954) Clinical reactions of schizophrenics to sodium amytal, pervitin hydrochloride, mescaline sulfate, and d-lysergic acid diethylamide (LSD25) *Journal of Nervous and Mental Disease,* 119, 95-112.	Sodium amytal 0.25 - 0.50 gm Pervitin hydrochloride 20 mg - 40 mg Mescaline sulfate 0.4 - 0.6 gm dLSD-25 0.010 - 0.120 mg	55 Schizophrenic patients received amytal, pervitin, and mescaline 28 males 27 females 25 of the 55 schizophrenic patients also received LSD-25	**Physiological** *Amytal* Central depression Sedation Hypnosis *Pervitin* Central stimulation *Mescaline & dLSD* Transient psychotic phenomena Commonly intensified symptoms **Psychological** Emotional lability Instability Depression Self-deprecation Shame Hostility Suspicion Tension Anxiety Auditory hallucinations Paranoia Euphoria Relaxation Sedation	"Normalization" in some patients - decreased symptomatology during drug experience, especially with amytal and pervitin, a small minority with dLSD-25 A small minority of subjects experienced nearly complete normalization under the influence of Amytal Diphasic response in some patients - mixture of aggravated symptoms and suppression of symptoms Intensification of pre-existing symptoms in some patients, especially with mescaline and dLSD-25

Sandison, R.A., Spencer, A.M., Whitelaw, J.D., 1954. The therapeutic value of lysergic acid diethylamide in mental illness. *J. Ment. Sci.* 100, 491e507. https://doi.org/10.1192/bjp.100.419.491.	dLSD-25 0.025 - 0.400 mg, administered regularly over the course of weeks or months	36 psychoneurotic patients observed over a period of 1 year	**Physiological** Disturbed or violent behavior Flushed face Fixed eyes Disturbance of menstrual function in some women Nausea Dizziness Warmth or coldness **Psychological** Increased emotional activity (giggling, laughing, crying) Distress Hallucinations Anxiety attack Depersonalization Detachment of the conscious self Obsessional reactions	Many patients re-lived repressed childhood memories while under the influence of LSD 25; experimenters used this as a treatment modality to help subjects process past traumas 14 patients "recovered" from their psychoneurotic condition, 3 improved, 2 not improved, 1 too early to assess results Clinicians concluded that LSD is an effective adjunct to psychotherapy for treating anxiety and mental tension, but only under controlled conditions with skilled staff and therapists
Denber, H.C.B., Merlis, S., 1955. Studies on mescaline I. Action in schizophrenic patients. *Psychiatr. Q.* 29, 421e429. https://doi.org/10.1007/BF01567467.	Mescaline Sulfate (0.5g)	25 Schizophrenic patients 18 female 7 male Age: 18-51yr.	**Physiological** Alpha wave frequency increase Sweating Nausea Vomiting **Psychological** Hallucinations Catatonic Withdrawal Depression Acute anxiety Tension/Panic	Mescaline induced psychotic symptoms in remission patients. Emotional reactions of patients preceded ideational reactions. Transitory increases in alpha wave activity were correlated to appearance of physiological changes. One hour following an increase in alpha wave activity, the majority of the patients experienced a decrease in mescaline-induced symptoms.

Cholden, L.S., Kurland, A., & Savage, C., (1955). Clinical reactions and tolerance to LSD in chronic schizophrenia. *Journal of Nervous Mental Disease*, 122, 211.	LSD (100-500 µg) Daily (2 weeks) Mescaline (100-500µg) used for reaction comparison	20 Schizophrenic patients Age: <40yr.	**Physiological** Crying/Screaming Frantic laughing Appetite loss **Psychological** Hallucinations Euphoria Mood swings Increased eroticism Hypochondria Depression	Resolved symptoms of catonic patients while under the influence of LSD. 2-3 days into daily LSD administration, tolerance to the drug developed. 4-6 days were estimated to reset LSD tolerance. Increasing dosage to 500µg did not allow patients to overcome tolerance. Cross-tolerance between LSD and mescaline tolerance was not observed. Similar symptoms were observed between LSD and Mescaline cases.
Merlis, S., 1957. The effects of mescaline sulfate in chronic schizophrenia. *J. Nerv. Ment. Dis.* 125, 432.	Mescaline Sulfate 0.50-0.75 gram	24 female schizophrenic patients Age: 29-58yr.	**Physiological** Accelerated pulse rate Facial flushing Blood pressure changes Pupillary dilation **Psychological** Anxiety Apprehension Hallucinations Delusions Sexual thoughts	One patient experienced significant improvement from her condition after the mescaline experience. Seven patients had partial temporary improvement in their condition. Sixteen patients showed no change.
Monroe, R. R., Heath, R. G., Mickle, W. A., & Llewellyn, R.C. (1957). Correlation of rhinencephalic electrograms with behavior: A Study of Humans Under the Influence of LSD and Mescaline.	d-LSD-25 50-200 µg 1-LSD-25 1000 µg (no clinical effect) Mescaline 400 - 500 mg	6 patients with chronically implanted intracranial electrodes 5 patients were diagnosed with varying levels of schizophrenia 1 patient suffered from paralysis agitans	**Physiological** Inappropriate laughing Restlessness Overactive Blurring of vision Pain in the shoulder and chest Nausea **Psychological** Anxiety Hostility Negativism	Experimenters used cortical leads to observe that there was a decrease in cortical alpha activity and an increase in fast activity in the beta range, thought to underlie symptoms of anxiety, overactivity Paroxysmal activity was observed in the

Electroencephalography and Clinical Neurophysiology, 9(4), 623–642. https://doi.org/10.1016/0013-4694(57)90084-6			Fear Emotional responsiveness Depression Hallucinations Alert Responsive Confused Agitation	hippocampal, amygdaloid, and septal regions and was attributed to psychotic behavior while under the influence of mescaline or d-LSD-25.
Pauk, Z. D., & Shagass, C. (1961). Some test findings associated with susceptibility to psychosis induced by lysergic acid diethylamide. *Comprehensive Psychiatry,* 2(4), 188–195. https://doi.org/10.1016/S0010-440X(61)80010-2	LSD 15-500 µg Min. of 3 injection per patient; Injection interval 2-40 days.	14 psychiatric patients Age: 19-37yr.	**Physiological** Pupillary dilation Increased patellar reflex response Increased systolic BP Poor motor dexterity **Psychological** Delusions Violent behavior Catatonia Disorientation Cognitive disorganization	7/14 patients experienced LSD-induced psychosis at high doses (500µg). No correlation found between age/sex and chance of induced psychosis. Physiological differences between psychotic and nonpsychotic reactors were not significant.
Chessick, R. D., Haertzen, C. A., & Wilker, A. (1964). Tolerance to LSD-25 in Schizophrenic Subjects: Attenuation of Effects on Pupillary Diameter and Kneejerk Threshold After Chronic Intoxication. *Archives of General Psychiatry*, 10(6), 653–658. https://doi.org/10.1001/archpsyc.1964.01720240107012	LSD-25 1.0µg, 1.5µg, 3.9µg/kg. LSD injected at varying intervals over the course of 99 days .	10 chronic schizophrenic patients Age: 30-55yr.	**Physiological** Pupillary dilation Decreased knee jerk threshold **Psychological** Delusions Hallucinations Catatonia	Psychotic and Nonpsychotic patients recorded to develop tolerance towards LSD-25. Increased LSD-25 dose at 3.9 µg/kg amplified the physiological responses relative to 1.0µg, 1.5µg dosage. Physiological symptoms decreased 6 days post treatment. No correlation found between age/sex and physiological changes.
Vanggaard, T. (1964). Indications and counter-indications for LSD treatment: Observations at Powick Hospital,	LSD 0-400µg 3 year long study Injections at	22 LSD users Age and Sex varied	**Physiological** Sweating Tachycardia Rigid/Cold feeling Facial flushing	Improved consciousness and confidence in fields of relationships, career, and self-acceptance after long term LSD treatment.

England. *Acta Psychiatrica Scandinavica, 40*(4), 427–437. https://doi.org/10.1111/j.1600-0447.1964.tb07495.x	varying intervals		**Psychological** Anxiety Depression Delusions Hallucinations Euphoric Déjà vu Hypochondria	Patients with mental disorders (schizophrenia, psychopathy, psychosis) showed greater degree negative symptoms. High ego of patients was correlated to positive LSD treatment outcomes, while low ego along psychopathological states correlated with negative/ineffective outcomes.
Tietz, W. (1967). Complications following ingestion of LSD in a lower class population. *California medicine*, *107*(5), 396.	LSD-25; inconsistent dosage due to self-administration of LSD Reported dosage ranged from 100µg-2000µg Most patients reported taking other various drugs in conjunction with LSD	49 patients observed over a 3 month period 27 male 12 female Majority under 25 years of age Patients admitted to the psychiatric unit of Los Angeles County Hospital due to complications from LSD ingestion	**Physiological** Panic reactions **Psychological** Reappearance of drug symptoms without re-ingestion of the drug Overt psychosis Acute anxiety reaction Hallucinations	57% of patients developed an extended psychosis state following their bad experience with LSD, despite them not having a psychotic history

Langs, R.J., Barr, H.L., 1968. Lysergic acid diethylamide (LSD-25) and schizophrenic reactions. *J. Nerv. Ment.* Dis. 147, 163.	LSD-25 Dosage unspecified Initial 2 weeks: Controlled, no drugs. Week 2: First Dose Week 5-6: Second Dose	52 LSD users and 29 matched schizophrenic patients. Age: 14-39yr. (Mean:20.5) White Male majority	**Physiological** Passivity **Psychological** Hallucinations -mainly auditory Delusions Depression Guilt feelings Suicidal thoughts Mental impairment	LSD patients relative to Schizophrenic patients had: - Less frequent delusions -Higher depressive characters LSD and Schizophrenic patients shared more symptomatic similarities than differences.
Tomsovic, M., Edwards, R.V., 1970. Lysergide treatment of schizophrenic and nonschizophrenic alcoholics: a controlled evaluation. *Q. J. Stud.* Alcohol 31, 932-949.	LSD 500µg Injections at varying intervals 1 year long study Data collected at 3,6,12 months post hospital discharge.	75 alcoholics (23 schizophrenics) Mean Age: 44yr	**Physiological** Prolonged Panic Confusion **Psychological** Delusions Psychosis Paranoia Suicidal thoughts Detachment of the conscious self Spiritual connections	Nonschizophrenic alcoholics showed a greater frequency of positive experiences, and greater chance of alcohol abstinence. LSD was not significant enough at treating alcoholism. LSD symptom recrudescence was more common in drinking patients versus abstrainres

Appendix B

Participant Demographics, Diagnoses and Psychotic Presentations

ID	PSYCH. DX	PSYCH. EXP.	FAM. PS. DX	AGE	GEN.	SEX. OR	RACE	REL/SPR?	REL/SPR CONT'D
1		DEL, OTR		28	Male	Heterosexual	White	Yes	Other
2		HAL, DEL, NEG		18	Female	Heterosexual	White	No	
3		HAL, DEL, NEG		25	Female	Bisexual	White	Yes	Other
4	PSD, PMD	HAL, DEL, NEG	PSD	34	Male	Pansexual	White	Yes	Other
5		HAL, DEL, NEG		18	Transgender	Bisexual	White	No	
6	PSD, PMD	HAL, DEL	PSD, PPD, PMD	25		Heterosexual	Black	No	
7	PMD, PSD, PPD, OPD	HAL, DEL, NEG	PPD, PMD	23	Female	Heterosexual	White	Yes	Other
8	PMD, PSD	HAL, DEL, NEG	PSD	27	Female	Queer	White	No	
9		DEL	PSD	28	Male	Heterosexual	Black	Yes	Buddhism
10		HAL, DEL, NEG		54	Male	Heterosexual	White	Yes	Buddhism
11	PMD	HAL, DEL		35	Male	Queer	Asian	Yes	Shinto
12	PSD	HAL, DEL, NEG		29	Female	Heterosexual	White	Yes	
13	PPD	HAL, DEL, NEG		62	Female	Other	White	Yes	Folk Religion
14		HAL, NEG		27	Male	Bisexual	White	No	
15	PPD, PMD	HAL, DEL, NEG		35	Female	Bisexual	White	No	
16	PMD, PSD	HAL, DEL, OTR	PSD, PPD,	41	Male	Bisexual	White	Yes	Christianity,Budd

			PMD						hism,Agnostic
17	PMD	HAL, DEL, NEG	PSD	34	Female	Bisexual	White	Yes	Christian Catholic
18	PSD	HAL, DEL		38	Male	Heterosexual	White	No	
19	PSD, PPD	HAL, DEL, NEG	PSD, PPD, PMD	27	Female	Heterosexual	White	Other:	
20	PPD	HAL, DEL, NEG		20	Transgender	Bisexual	White	Yes	Agnostic
21	PSD, PMD	HAL, DEL		25	Male	Heterosexual	Latinx/Hisp/Span.	Yes	Agnostic,Other
22	OPD	HAL, DEL		31	Transgender	Other	White	Other:	
23	PSD, PMD	HAL, DEL, NEG	PSD	28	Male	Heterosexual	White	Other:	
24	PSD, PMD	HAL, DEL, NEG, OTR	PSD, PMD	25	Female	Heterosexual	White	Yes	Other
25	PSD, PMD	HAL, DEL, NEG	PMD	19	Female	Bisexual	Indigenous	Other:	
26		HAL, NEG	PMD	18	Male	Heterosexual	White	Yes	Buddhism,Hindu
27		HAL, DEL, NEG	PPD, PMD	18	Male	Heterosexual	White	Other:	
28		HAL, DEL, NEG		19	Male	Bisexual	White	No	
29	PMD	DEL	PSD	24	Male	Bisexual	White	Yes	Other
30	PSD	HAL, DEL, NEG		41	Female	Heterosexual	White	No	
31	PSD	DEL, NEG		22	Female	Bisexual	Latinx/Hisp/Span.	Other:	
32	PMD	HAL, DEL, NEG	PMD	21	Male	Heterosexual	White	Yes	Christianity
33	PMD	HAL, DEL, NEG		33	Male	Heterosexual	White	Yes	Other
34	PMD	DEL	PSD, PMD	49	Male	Heterosexual	Latinx/His	Yes	Buddhism

							p/Span.		
35		HAL, DEL		19	Male	Bisexual	White	Other:	
36	PSD	HAL, DEL, NEG	PSD	25	Male	Bisexual	Mixed	No	
37	PSD, PPD	HAL, DEL, NEG		33	Female	Heterosexual	White	No	
38	PSD	DEL	PSD	23	Male	Heterosexual	Middle Eastern	Yes	Islam
39	PMD	DEL, NEG		27	Male	Gay/Lesbian	White	Yes	Agnostic
40	OPD	HAL, DEL, NEG	PSD	23	Female	Heterosexual	White	No	
41	PSD	HAL, DEL, NEG		20	Male	Heterosexual	Asian	Yes	
42	PMD	DEL, NEG	PSD	22	Female	Bisexual	Mixed	Yes	Atheist
43	PMD, PPD	HAL, DEL, NEG		20	Male	Gay/Lesbian	Mixed	Yes	Other
44		DEL	PMD	19	Male	Heterosexual	White	No	
45	PSD	DEL, NEG	PMD	45	Male	Heterosexual	White	Other:	
46	OPD	HAL, DEL, NEG	PMD	25	Female	Heterosexual	White	No	
47		DEL		28	Female	Bisexual	Asian	Yes	Christian Catholic,Agnostic
48	OPD	HAL, DEL, NEG	PSD, PMD	32	Two-Spirit	Pansexual	Indigenous	Yes	Other
49	PSD, PMD, PPD	HAL, DEL, NEG	PSD, PMD	18	Male	Bisexual	White	No	
50	PSD, PMD	HAL, DEL, NEG	PSD, PMD	25	Male	Heterosexual	Indigenous	Yes	Atheist
51	PSD	DEL		42	Male	Heterosexual	White	Yes	Buddhism
52	PSD	HAL, DEL, NEG	PSD, PPD, PMD	25	Female	Bisexual	Pacific Islander	No	

53	OPD, PMD	HAL, DEL, NEG, OTR	PSD	18	Female	Queer	White	Other:	
54	PPD, PMD	HAL, DEL, NEG	PMD	40	Male	Heterosexual	White	No	
55	PSD	DEL, NEG		38	Male	Heterosexual	White	Yes	Other
56	PMD	HAL, DEL		22	Non-binary	Queer	White	Other:	
57		DEL, NEG	PMD	18	Male	Heterosexual	White	Yes	
58	PMD, PPD	HAL, DEL, NEG	PMD, PSD	19	Female	Bisexual	Latinx/Hisp/Span.	Yes	Buddhism
59	PPD, PMD	HAL, DEL		40	Male	Prefer not to say	White	Yes	Buddhism,Atheist, Agnostic
60	UPD	HAL, DEL, NEG	UPD	27	Male	Bisexual	White	No	
61	PMD, OPD	HAL, DEL, NEG		30	Female	Heterosexual	White	No	
62	PMD	HAL, DEL, NEG		23	Male	Bisexual	White	Other:	
63	PSD	HAL, DEL, NEG		52	Male	Heterosexual	White	No	
64	OPD	HAL, DEL, NEG		22	Transgender	Gay/Lesbian	White	Yes	Judaism
65	PMD, PPD	HAL, DEL, NEG	PMD	31	Female	Heterosexual	White	Yes	Other
66	PMD	HAL, DEL, NEG		30	Female	Bisexual	White	No	
67	PPD	HAL, DEL, NEG		24	Transgender	Bisexual	White	No	
68	UPD	DEL, NEG		38	Female	Heterosexual	White	Other:	
69	PMD	DEL, NEG		37	Female	Other	White	No	
70	PPD	HAL, DEL, NEG	PMD, PPD	29	Two-Spirit	Bisexual	Indigenous	No	
71	UPD	HAL, DEL, NEG		35	Female	Bisexual	White	Yes	

72	UPD, PPD, OPD	HAL, DEL, NEG		27	Transgender	Queer	White	Other:	
73	PMD	HAL, DEL, NEG	PPD	20	Non-binary	Bisexual	White	Yes	Folk Religion,Other
74	PSD	HAL, DEL, NEG	UPD	23	Male	Heterosexual	Mixed	No	
75	PMD	HAL, DEL, NEG		18	Female	Heterosexual	White	Yes	Other
76	PMD	HAL, DEL, NEG		45	Female	Bisexual	Mixed	Yes	Folk Religion,Agnostic
77	PSD	HAL, DEL, NEG		34	Female	Heterosexual	White	No	
78	PSD	HAL, DEL, NEG		19	Male	Heterosexual	White	Yes	Agnostic
79	UPD	HAL, DEL, NEG		23	Non-binary	Bisexual		Yes	Buddhism,Folk Religion
80	PPD, PMD	HAL, DEL, NEG	PMD	21	Male	Gay/Lesbian	White	Yes	Judaism
81	PSD	HAL, DEL, NEG	UPD	27	Male	Gay/Lesbian	White	No	
82		HAL, DEL, NEG		19	Other	Gay/Lesbian	White	Other:	
83		DEL, NEG		24	Male	Heterosexual	White	No	
84		DEL, NEG		26	Male	Bisexual	White	No	
85		HAL, DEL		23	Male	Queer	White	No	
86		HAL, DEL, NEG		32	Female	Heterosexual	White	No	
87		DEL, NEG		31	Male	Heterosexual	White	Yes	Agnostic,Other
88		DEL, NEG		18	Male	Heterosexual	White	No	
89		HAL, DEL, NEG		18	Male	Heterosexual	White	Other:	
90		DEL, NEG		20	Male	Heterosexual	White	Yes	Agnostic
91		HAL, DEL, NEG		21	Male	Heterosexual	White	Yes	Agnostic

92	DEL, NEG	20	Female	Queer	Black	Yes	Other
93	DEL, NEG	23	Male	Heterosexual	White	Other:	
94	HAL, DEL, NEG	22	Female	Bisexual	White	Yes	
95	HAL, DEL, NEG	26	Female	Bisexual	White	No	
96	DEL, NEG	25	Male	Heterosexual	Latinx/Hisp./Span.	No	
97	HAL, DEL	25	Male	Heterosexual	Latinx/Hisp./Span.	Yes	Christianity
98	DEL, NEG	23	Female	Bisexual	White	Yes	Buddhism
99	DEL, NEG	47	Female	Heterosexual	White	No	
100	DEL, NEG	22	Male	Heterosexual	White	Yes	Christian Catholic

Note. Participants 1-59 completed the second survey and participants 60-100 completed the first survey. For coding purposes, psychotic diagnosis was categorized into five groups: Psychotic spectrum disorder (PSD), Psychotic mood disorder (PMD), Psychotic personality disorder (PPD), Other psychotic disorders (OPD), and Unspecified psychotic disorder (UPD). Symptoms were coded into four categories: Hallucinations (HAL), Delusions (DEL), Negative symptoms (NEG), and Other (See Appendix A). It is important to note that individuals who had more than one diagnosis or symptom per group/category were only coded once per group/category. In addition, individuals who added "other" and provided responses such as "I don't know" in response to their psychotic symptoms were not coded as "Other" and were removed. Rel / Spr Cont'd indicates the respondents' identified affiliation with a religious or spiritual tradition.

Appendix C

Participant Experiences of Psychedelic Drug Use

ID	Psychedelic	MDMA	NCA	CAN	RX	OTR	Dose	Comfortable Setting?	Personal Growth?	Increased Spirituality?	Memories of Life Events?	MEQ	LOVE	Resilient
1	PSL						High	Somewhat	Yes	Yes	Yes	8.3	--	10
2	PSL	X					Medium	Yes	Yes	Yes	Yes	8.3	10	6
3	MIX						Medium	Yes	Yes	Yes	Yes	8.6	10	10
4	LSD						Medium	Somewhat	Yes	Yes	Yes	10.0	--	10
5	MDMA						Medium	Somewhat	Yes	No	Somewhat	2.9	2	1
6	LSD		X				High	Yes	Somewhat	Same	Yes	8.5	10	4
7	MDMA				X		Medium	No	No	Yes	Somewhat	5.2	5	5
8	KTM				X		High	Yes	Yes	Yes	Yes	7.7	10	10
9	AYA						Unsure	Yes	Somewhat	Yes	Yes	7.7	8	7
10	LSD		X	X			High	No	Yes	Yes	Yes	7.6	--	
11	DMT						High	Yes	Somewhat	Yes	Yes	3.7	4	4
12	PSL						Medium	Yes	Yes	Yes	Somewhat	6.3	8	9
13	PSL						Low	Yes	Somewhat	Yes	No	--	--	2
14	PSL		X				Medium	Yes	Somewhat	Yes	No	7.9	7.5	7

15	KTM				X		Medium	Yes	Somewhat	No	No	--	--	3
16	LSD		X		X		Medium	Yes	Yes	Yes	Yes	7.8	3	7
17	LSD						Medium	Yes	Yes	Yes	No	8.6	--	2
18	PSL						High	Yes	Yes	Yes	Somewhat	--	2	7
19	LSD						Unsure	Yes	Yes	Same	No	--	8.5	10
20	PSL						Medium	No	Somewhat	Yes	No	4.6	0	6
21	LSD	X		X	X		Medium	Yes	Yes	Yes	Yes	--	10	10
22	PSL						High	Somewhat	Yes	Yes	No	--	10	
23	PSL						High	Yes	Yes	Same	No	6.1	5.5	5
24	MDMA						High	Somewhat	Yes	Yes	Somewhat	--	--	6
25	LSD				X		High	Somewhat	Somewhat	Yes	Yes	8.3	8.5	8
26	LSD						High	Yes	Somewhat	Yes	Yes	6.8	5.5	1
27	PSL		X	X			High	Yes	Yes	Yes	Yes	--	--	7
28	PSL						High	Somewhat	Yes	Yes	Somewhat	6.6	0	7
29	MIX					X	High	Somewhat	Somewhat	Yes	Yes	6.1	3.5	9
30	LSD	X	X				High	Somewhat	Somewhat	No	No	8.9	2	6
31	PSL						High	Somewhat	Yes	Yes	Yes	--	10	10
32	LSD			X	X		High	Yes	Yes	Yes	Yes	10.0	10	10

33	LSD					High	Yes	Yes	Yes	Yes	9.6	0	0
34	PSL		X	X		Medium	Yes	Yes	Yes	Yes	7.9	8.5	9
35	PSL					High	Yes				--	--	
36	LSD			X		Medium	Somewhat	Yes	Yes	Yes	7.2	6	
37	LSD					Unsure	Yes	Yes	Yes	Yes	--	6	6
38	LSD					Medium	Yes				--	--	
39	PSL		X	X	X	Medium	Yes	Yes	Yes	Yes	7.2	7	10
40	KTM	X			X	Unsure	Somewhat	Somewhat	Same	No	--	10	10
41	PSL					Medium	No				--	--	
42	PSL			X		Medium	Yes	Yes	Yes	Yes	6.9	9	9
43	LSD		X	X		High	Somewhat	Yes	Yes	Yes	--	9.5	10
44	PSL					High	Somewhat	Yes	Yes	Yes	--	--	5
45	PSL		X		X	High	Yes	Yes	Yes	Somewhat	7.5	8.5	8
46	PSL					Low	Yes	No	Same	Somewhat	--	1.5	
47	PSL					Medium	Somewhat	Somewhat	No	No	4.1	1.5	1
48	LSD		X	X		Medium	Somewhat	Yes	Yes	Somewhat	9.4	8.5	7
49	LSD					Medium	Yes	Somewhat	Yes	No	8.6	7	6
50	PSL		X	X		Medium	Yes	Somewhat	Yes	Yes	7.6	8.5	4

51	PSL						Medium	Yes	Somewhat	Same	Yes	--	--	7
52	KTM				X		Medium	Yes	Yes	Yes	Yes	8.8	4.5	10
53	PSL		X				High	Somewhat	Yes	Same	Yes	7.4	8.5	9
54	PSL		X	X			N/A	Yes	Yes	Yes	Somewhat	8.6	--	
55	LSD		X			X	High	Somewhat	Yes	Yes	Yes	7.7	6.5	5
56	PSL					X	Medium	Yes	Yes	Same	Yes	--	4.5	10
57	MIX						Unsure	Yes	Yes	Yes	Yes	7.1	7.5	10
58	PSL						Medium	Yes	Yes	Yes	Yes	9.1	10	10
59	LSD	X		X			Medium	Yes	Yes	No	Somewhat	--	8.5	8
60	PSL			X			High	Yes	Yes	Yes	Somewhat	9.5	9	8
61	PSL	X			X		High	Somewhat	Yes	Yes	Yes	10.0	5	0
62	LSD		X	X	X		High	Somewhat	Yes	Yes	Yes	10.0	9	10
63	LSD		X	X	X		High	No	No	No	No	--	--	
64	LSD					X	Medium	Yes	Yes	Same	Yes	--	6	8
65	PSL			X			Low	Yes	Yes	Yes	Yes	--	10	10
66	LSD		X	X		X	Medium	Yes	Yes	Yes	No	--	5	
67	LSD				X		High	Somewhat	Somewhat	Yes	Yes	3.1	1.5	2
68	PSL			X		X	Unsure	Yes	No	No	Yes	--	--	

69	LSD		X		X		Medium	Somewhat	Yes	Yes	Yes	4.6	7	8
70	LSD				X		High	Somewhat	No	No	Somewhat	--	--	
71	PSL						Medium	Somewhat	Yes	Same	Yes	8.6	1.5	1
72	LSD						Medium	Somewhat	No	Same	Somewhat	--	2.5	7
73	KTM			X		X	Unsure	Somewhat	Somewhat	Yes	No	--	--	1
74	LSD		X				High	Somewhat	No	Yes	No	--	0	5
75	PSL						Low	Yes	Somewhat	Yes	Somewhat	--	9	9
76	PSL						Medium	Yes	Yes	Yes	No	5.6	6.5	7
77	KTM						High	Yes	Yes	Yes	Yes	--	10	10
78	LSD			X			High	Yes	Somewhat	Same	No	3.9	2	4
79	PSL				X		High	Somewhat	Somewhat	Yes	Yes	--	--	
80	LSD	X	X			X	High	Somewhat	No	No	No	--	--	
81	PSL							Somewhat	Somewhat	Same	Yes	--	10	10
82	LSD						Medium	Yes	Yes	Yes	Somewhat	9.0	5.5	8
83	PSL		X	X			High	Yes	Yes	Same	No	9.0	7.5	5
84	PSL						High	Yes	Somewhat	No	No		--	10
85	PSL						Medium	Yes	No	Same	No	1.0	0	0
86	LSD				X		Medium	Yes	Somewhat	Same	No	5.0	10	2
87	PSL						Medium	Yes	Yes	Yes	Yes	10.0	7.5	8

88	LSD						High	Somewhat	Somewhat	No	Somewhat	4.0	5	9
89	PSL		X			X	Unsure	No	Somewhat	Yes	No	2.0	4.5	7
90	MIX		X	X			Medium	Yes	Yes	Yes	No	8.0	7.5	7
91	LSD			X			Medium	Yes	Yes	Yes	Yes	6.0	2	8
92	PSL		X	X			Medium	Yes	Somewhat	Same	Yes	5.0	2.5	10
93	DMT			X			Medium	Yes	Yes	Yes	No		--	
94	BOH-2CB						High	Yes	Yes	Yes	Somewhat	7.0	10	7
95	PSL					X	Medium	Yes	Yes	No	Somewhat	8.0	--	8
96	LSD	X	X	X			Medium	Somewhat	Yes	Yes	Yes	3.0	3	4
97	MIX						High	Yes	Yes	Yes	Yes	10.0	7.5	7
98	LSD				X		Medium	Yes	Yes	Yes	Yes	5.0	5.5	5
99	MIX						Medium	Yes	Yes	Yes	Yes	10.0	10	10
100	LSD				X		High	Yes	Somewhat	No	No	4.0	5.5	1

Note. This table depicts individuals' use of psychedelic drugs, combinations, dose, and other relevant variables regarding reported psychedelic experiences. In addition, the table shows whether individuals reported their experience as resulting in personal growth, comfortability in setting, whether their experience resulted in increased spirituality or contemplation. Items were on a 10-point Likert scale. 'Resilient' score was derived from the item, "The psychedelic experience I had helped me to feel more resilient towards life failures"; 'Memories of Life' score was derived from the item, "Did you establish a better understanding of past events, memories, traumatic experiences, that played a significant role in your life?" The 'Love scale' was developed from the items: "The psychedelic experience I had helped me to feel more loved and appreciated by the world around me; and the psychedelic experience I had helped me to feel more loved and appreciated by my family and friends.

Appendix D

Survey

Q117
Please fill out each question to the best of your ability. The survey should take approximately 15 to 20 minutes to complete. We thank you very much for your participation and help in advancing psychedelic science and mental health research.

End of Block: Informed Consent

Start of Block: Perquisites

Q230
We're going to ask you some questions about psychotic symptoms BEFORE or AFTER your psychedelic use and not during it as these are typical experiences while on psychedelics.

1. Do you believe you have ever had a psychotic experience of any kind? Examples **may include** hearing voices that other people do not, seeing things that other people do not, having beliefs that others consider odd or strange, feeling disconnected to your body, etc.

- ○ Yes
- ○ No

Skip To: End of Survey If Do you believe you have ever had a psychotic experience of any kind? Examples may include hearing... = No

Q222 Have you ever been diagnosed with one or more of the following conditions **by a healthcare professional?**

- ☐ Schizophrenia
- ☐ First Episode Psychosis
- ☐ Brief Psychosis
- ☐ Schizotypal Personality Disorder
- ☐ Schizoaffective Personality Disorder
- ☐ Schizoid Personality Disorder
- ☐ Bipolar Disorder with Psychotic Features
- ☐ Major Depressive Disorder with Psychotic Features
- ☐ Psychosis Not Otherwise Specified
- ☐ Other _____
- ☐ None of the Above

Display This Question:

If Do you believe you have ever had a psychotic experience of any kind? Examples may include hearing... = Yes

Q223 Have you ever had one or more of the following experiences?

- [ ] Hear voices or see things other people do not
- [ ] Smell or feel things other people do not
- [ ] Feel as if you are an extremely important or special persons
- [ ] Feel as if you are disconnected or detached from your body
- [ ] Feel as if others are conspiring or plotting against you or that people are out to get you
- [ ] Feel as if you can read other people's minds or that they can read yours
- [ ] Feel as if ordinary things such as a song on the radio or a billboard are speaking to you
- [ ] Other _____

Display This Question:

If Do you believe you have ever had a psychotic experience of any kind? Examples may include hearing... = Yes

Q239 Have you experienced one or more traumatic events in your lifetime?

- ○ Yes
- ○ No
- ○ Unsure

Display This Question:

If Have you experienced one or more traumatic events in your lifetime? = Yes

Or Have you experienced one or more traumatic events in your lifetime? = Unsure

Q240 Please elaborate.

_____

Display This Question:

If Do you believe you have ever had a psychotic experience of any kind? Examples may include hearing... = Yes

Q236 In addition, have you ever been diagnosed with one or more of the following conditions **by a healthcare professional?**

- ☐ Anxiety _____
- ☐ Depression _____
- ☐ Mood Disorder _____
- ☐ Personality Disorder _____
- ☐ Neurodevelopmental Disorder _____
- ☐ Other: _____

Display This Question:

If Do you believe you have ever had a psychotic experience of any kind? Examples may include hearing... = Yes

Q227 Has a family member ever been diagnosed with one or more of the following conditions **by a healthcare professional**?

- ☐ Schizophrenia
- ☐ First Episode Psychosis
- ☐ Brief Psychosis
- ☐ Schizotypal Personality Disorder
- ☐ Schizoaffective Personality Disorder
- ☐ Schizoid Personality Disorder
- ☐ Bipolar Disorder with Psychotic Features
- ☐ Major Depressive Disorder with Psychotic Features
- ☐ Psychosis Not Otherwise Specified
- ☐ Other _____
- ☐ None of the Above

Display This Question:

If Do you believe you have ever had a psychotic experience of any kind? Examples may include hearing... = Yes

Q228 Has a family member ever had one or more of the following experiences?

- [ ] Hear voices or see things other people do not
- [ ] Smell or feel things other people do not
- [ ] Feel as if you are an extremely important or special persons
- [ ] Feel as if you are disconnected or detached from your body
- [ ] Feel as if others are conspiring or plotting against you or that people are out to get you
- [ ] Feel as if you can read other people's minds or that they can read yours
- [ ] Feel as if ordinary things such as a song on the radio or a billboard are speaking to you
- [ ] Other _____

Display This Question:

If Do you believe you have ever had a psychotic experience of any kind? Examples may include hearing... = Yes

Q238 In addition, has a family member ever been diagnosed with any other conditions by a healthcare professional?

- ○ Yes
- ○ No
- ○ Unsure

Display This Question:

If In addition, has a family member ever been diagnosed with any other conditions by a healthcare pr... = Yes

Q237 If yes, with which one, or more, of the following conditions?

- [ ] Anxiety _____
- [ ] Depression _____
- [ ] Mood Disorder _____
- [ ] Personality Disorder _____
- [ ] Neurodevelopmental Disorder _____
- [ ] Other: _____

Page Break

2. Have you ever had a psychedelic experience of any kind? Examples may include taking LSD or “acid”, psilocybin or "magic mushrooms", MDMA or "ecstasy", Ketamine, DMT, etc.

- ○ Yes
- ○ No

Skip To: End of Survey If Have you ever had a psychedelic experience of any kind? Examples may include taking LSD or “acid”... = No

Q198 What is your age?

_____

Skip To: End of Survey If Condition: What is your age? Is Less Than or Equal to 17. Skip To: End of Survey.

End of Block: Perquisites

Start of Block: Demographics

Q134
Before getting started, we would like to know a little bit about who is taking our survey. We thank you very much for your participation and help in advancing psychedelic science and mental health research.

Page Break

2. Gender:

- ○ Male
- ○ Female
- ○ Non-binary
- ○ Transgender
- ○ Two-Spirit
- ○ Other: _____

Q189 Height (please only select your preference):

- ○ Centimeters _____
- ○ Feet/Inches _____
- ○ Unsure
- ○ Prefer not to say

Q190 Body Weight (please only select your preference):

- ○ Kilograms _____
- ○ Pounds _____
- ○ Unsure
- ○ Prefer not to say

3. Sexual Orientation:

- ○ Heterosexual
- ○ Gay/Lesbian
- ○ Bisexual
- ○ Queer
- ○ Pansexual
- ○ Other _____
- ○ Prefer not to say

4. Race/Ethnicity:

- ○ White
- ○ Middle Eastern
- ○ Indigenous
- ○ Asian
- ○ Pacific Islander
- ○ Hispanic, Latino, or of Spanish Origin
- ○ Black
- ○ Other: _____

5. Country of Residence:

- ○ United States
- ○ Canada
- ○ Mexico
- ○ Other: _____

6. What is the highest level of education you completed?

- ○ High School, GED, or equivalent
- ○ College
- ○ Graduate/professional school
- ○ Other _____

7. Religious or Spiritual:

- ○ Yes
- ○ No
- ○ Other: _____

Display This Question:

If Religious or Spiritual: = Yes

8. If yes, what religion do you practice? Please select all that apply:

- ☐ Christianity
- ☐ Christian Catholic
- ☐ Judaism
- ☐ Islam
- ☐ Shinto
- ☐ Sikhism
- ☐ Buddhism
- ☐ Confucianism
- ☐ Jainism
- ☐ Hindu
- ☐ Zoroastrianism
- ☐ Folk Religion
- ☐ Atheist
- ☐ Agnostic
- ☐ Other _____

End of Block: Demographics

Start of Block: Preliminary Questions

Q179
Now we are going to further ask you about your mental health, psychological functioning, and emotional well-being BEFORE or AFTER your psychedelic use.

Page Break

2. What are your chief complaints in regard to your mental health? Please limit response to 100 words maximum.

_____

JS

3. When did your symptoms begin and how long did they last? Please limit response to 100 words maximum.

_____

5. Have you ever received psychotherapy?

- Yes
- No
- N/A

Display This Question:

If Have you ever received psychotherapy? = Yes

JS

5.1 If so, please state what kind, what for and from when to when? Please limit response to 100 words maximum.

_____

End of Block: Preliminary Questions

Start of Block: Davis Psychedelic Questionnaire

Q188
Now we are going to ask you some questions about your experiences with psychedelic drugs.

Page Break

2. **Think of a SINGLE time when you did a psychedelic (or combination of psychedelics at once) that was most memorable. Please keep that experience in mind when answering the next few questions.**

Which psychedelics did you take at that time? Please check all that may apply:

- [ ] Psilocybin
- [ ] LSD
- [ ] Iboga/Ibogaine
- [ ] Ayahuasca
- [ ] N,N-DMT
- [ ] 5-MeO-DMT
- [ ] Mescaline
- [ ] MDMA
- [ ] Peyote Cactus
- [ ] Ketamine
- [ ] Other: _____

Q191 Dosage level:

- ○ High
- ○ Medium
- ○ Low
- ○ Unsure of Dosage
- ○ N/A

3. Specific dosage including form of measurement if remembered:

_____

Page Break

4. How old were you when you had this experience?

_____

Q219 Were you in an active psychotic episode at the time of taking the psychedelic?

- Yes
- No

Display This Question:

If Were you in an active psychotic episode at the time of taking the psychedelic? = Yes

Q229 Please elaborate and limit response to 100 words maximum.

_____

Q221 What was your reason for taking the psychedelic?

- [ ] Recreation
- [ ] Self-Growth/Discovery
- [ ] To help manage mental health symptoms
- [ ] Other _____

5. How many years ago?

() 

6. How well do you remember it?

- ○ Very well
- ○ Well
- ○ Somewhat
- ○ Not well

7. Method of Psychedelic consumption:

- [ ] Smoked
- [ ] Swallowed/Ingested
- [ ] Vaporized
- [ ] Snorted
- [ ] Intravenous injection
- [ ] Intramuscular Injection
- [ ] Other _____

8. Duration of the psychedelic experience?

- ○ 30 minutes to an hour
- ○ 1 to 3 hours
- ○ 3 to 6 hours
- ○ 6 to 12 hours
- ○ > 12 hours

9. Were you under the influence of any psychoactive substances prior to taking the psychedelic(s)?

- ○ Yes
- ○ No
- ○ Unsure
- ○ Prefer not to say

Display This Question:

If were you under the influence of any psychoactive substances prior to taking the psychedelic(s)? = Yes

9.1 If yes, which substances? Select all that apply:

- [ ] Alcohol
- [ ] Nicotine
- [ ] Caffeine
- [ ] MDMA
- [ ] Classic Psychedelics (e.g., psilocybin, LSD, 5-MeO-DMT)
- [ ] Cannabis/Marijuana (any form)
- [ ] Amphetamines
- [ ] Opiates
- [ ] Dissociative Anesthetics
- [ ] Inhalants
- [ ] Cocaine
- [ ] Benzodiazepines
- [ ] Barbiturates
- [ ] Other _____

Q196 Were you taking any prescription medications within three days prior of your psychedelic experience?

- ○ Yes
- ○ No
- ○ Unsure
- ○ Prefer not to say

Display This Question:

If Were you taking any prescription medications within three days prior of your psychedelic experience? = Yes

Q197 If yes, please select all that may apply:

- ☐ SSRIs
- ☐ Antidepressants
- ☐ Antipsychotics
- ☐ Anti-anxietys
- ☐ Other: _____

10. Mood **immediately** prior to taking psychedelic(s):

- [ ] Fear
- [ ] Anger
- [ ] Shame/Disgust
- [ ] Sadness
- [ ] Confusion
- [ ] Surprised
- [ ] Interested/Curious
- [ ] Happiness
- [ ] Joyful/Giddy
- [ ] Awe/Inspired
- [ ] Serene
- [ ] Grateful
- [ ] Other _____

JS *

11. Please elaborate and limit response to 100 words maximum.

_____

12. Did you feel comfortable and safe in the environment you took the psychedelic?

- ○ Yes
- ○ Somewhat
- ○ No

JS ✱

13. Please elaborate and limit response to 100 words maximum.

_____

14 Did you take the psychedelic by yourself?

- ○ Yes
- ○ No

Display This Question:

If DId you take the psychedelic by yourself? = No

15. Did you take the psychedelic in a group setting?

- ○ Yes
- ○ No

JS ✱

Q184 Please elaborate and limit response to 100 words maximum.

_____

JS *

14. What was your expectation for the psychedelic experience? Please limit response to 100 words maximum.

_____

JS *

15. How did you feel during the experience? Please limit response to 100 words maximum.

_____

_____

_____

_____

_____

Q238 During my psychedelic experience, my symptoms got...

- ○ Worse
- ○ Better
- ○ Stayed the same
- ○ Didn't notice
- ○ N/A

Q241 Please elaborate within 100 words or less.

_____

16. How did you feel immediately after the experience? Please limit response to 100 words maximum.

_____

Page Break

17. **The next questions are in regard to the few days following the psychedelic experience you had:**

Q239 After my psychedelic experience, my symptoms got...

- ○ Worse
- ○ Better
- ○ Stayed the same
- ○ Didn't notice
- ○ N/A

Q242 Please elaborate within 100 words or less.

_____

Q240 Did your relationship with your symptoms change?

- Yes
- No
- Stayed the same
- N/A

Q243 Please elaborate within 100 words or less.

_____

Page Break

Q192 Did you receive any psychotherapy after your experience?

- Yes
- No
- N/A

Display This Question:

If Did you receive any psychotherapy after your experience? = Yes

18. If so, what was your comfort level talking and delving deeper into your mind with the assistance of a therapist:

- Low
- Medium
- High

19. Did you feel your psychedelic experience resulted in personal growth?

- ○ Yes
- ○ Somewhat
- ○ No

JS *

Q201 Please elaborate and limit response to 100 words maximum.

_____

20. Did you feel deeper levels of spirituality or contemplation?

- ○ Yes
- ○ No
- ○ Remained the same

JS *

21. Please elaborate and limit response to 100 words maximum.

_____

22. Did you feel more connected to the earth and the life on it?

- ○ Yes
- ○ Somewhat
- ○ No

JS *

23. Please elaborate and limit response to 100 words maximum.

_____

24. Did you establish a better understanding of past events, memories, traumatic experiences, that played a significant role in your life:

- ○ Yes
- ○ Somewhat
- ○ No

JS *

Q202 Please elaborate and limit response to 100 words maximum.

_____

25. Did you become more comfortable with the meaning of life:

- ○ Yes
- ○ Somewhat
- ○ No

JS *

Q203 Please elaborate and limit response to 100 words maximum.

_____

26. Did you gain a deeper understanding of perspectives surrounding family, friends, and people around me:

- ○ Yes
- ○ Somewhat
- ○ No

JS *

Q204 Please elaborate and limit response to 100 words maximum.

_____

Page Break

Q180
These next few questions will be regarding the next few days following your psychedelic experience. Please bear that in mind when responding.

Page Break

27. Several days following the experience, Career and passion appeared more reachable:

- ○ Yes
- ○ Somewhat
- ○ No

28. Several days following the experience, I felt self-love:

- ○ Yes
- ○ Somewhat
- ○ No

29. Several days following the experience, I realized thoughts that I usually have probably aren't true:

- ○ Yes
- ○ Somewhat
- ○ No

---

30. Several days after the experience, did you feel any abnormal physical side effects? Select all that may apply.

- ☐ Throwing up
- ☐ Itching
- ☐ Spasms
- ☐ Yawning
- ☐ Other _____
- ☐ None

End of Block: Davis Psychedelic Questionnaire

Start of Block: Mystical Experience Questionnaire (MEQ-20)

Q174

The following questions are to be answered in response to how you were feeling DURING your psychedelic experience. These items are on scale of 0-10 with 0 meaning not at all and 10 meaning absolutely yes.

Page Break

1. During the psychedelic experience I …

	0 1 2 3 4 5 6 7 8 9 10
I saw a higher power	
I encountered the ultimate/true reality	
I experienced unity with ultimate reality	
I felt free of personal limitations allowing me to be greater than myself	
I felt more peaceful	
I felt joyful	
I felt amazing	
I lost the sense of time	
I lost the sense of space	
I felt the world of no space boundaries	
I cannot fully describe the experience in words	

End of Block: Mystical Experience Questionnaire (MEQ-20)

Start of Block: Self Compassion/Love

Q181

The following questions are to be answered in response to how you were feeling about love during and after the psychedelic experience you had. These items are on a scale of 0-10 with 0 meaning not at all and 10 meaning absolutely yes.

Page Break

1. The psychedelic experience I had helped me to…

	0 1 2 3 4 5 6 7 8 9 10
Feel more loved and appreciated by the world around me	
Feel more loved and appreciated by my family and friends	
Feel more passionate towards my career goals	
Feel more comfortable with my life purpose	
Feel more resilient towards life failures	

End of Block: Self Compassion/Love

Start of Block: Qualitative Data

JS ✱

1. In summary, how would you describe your psychedelic experience you had overall? Please limit response to 100 words maximum.

_____

_____

_____

_____

_____

JS ✱

Q195 Is there anything that you would like to mention about the experience that you feel was not captured by the questions answered. Please limit response to 100 words maximum.

_____

End of Block: Qualitative Data

Start of Block: Mental Health Resources

Q205
THANK YOU VERY MUCH FOR PARTICIPATING IN OUR SURVEY! Here are some free resources should you feel that you would like to speak with a mental health professional:

Q172 **Mental Health Crisis Line**
613-722-6914, 1-866-996-0991 (Toll Free), crisisline.ca
If you are experiencing a mental health crisis yourself, or you know someone who is, please phone the 24-Hour Mental Health Crisis Line.

Centre for Suicide Prevention
1-833-456-4566, www.crisisservicescanada.ca
If you're thinking about suicide or are worried about a friend or loved one, the Canada Suicide Prevention Service is available 24/7 for voice and 4 pm to 12 am ET for text.

Canada Drug Rehab Addiction Services Directory
1-877-746-1963, www.drugrehab.ca
Drug Rehab Services is a free resource for drug and alcohol addiction in Canada.

Psychology Today Therapist Directory
Website: www.psychologytoday.com/ca/therapists
Provides contact information for therapists, psychiatrists, therapy groups and treatment facility options.

Fireside Project Psychedelic Peer Support Line
1-62-Fireside (623-473-4733), https://firesideproject.org/
Provides real-time, free, confidential peer support by phone and text message to people in the midst of psychedelic experiences.

SAMHSA's National Helpline
1-800-662-HELP(4357) (Toll Free), https://samhsa.gov/find-help/national-helpline
SAMHSA's National Helpline, is a confidential, free, 24-hour-a-day, 365-day-a-year, information service, in English and Spanish, for individuals and family members facing mental and/or substance use disorders.

End of Block: Mental Health Resources