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ABSTRACT

Mesoamerican cultures utilized the power of entheogenic substances for hundreds of years before the scientific interest in psilocybin - a natural growing, hallucinogenic mushroom. In the brief time before federal criminalization, psilocybin was used in a number of studies and trials that demonstrated therapeutic potential. Once psilocybin gained popularity for recreational use in the 1960s counterculture, the Controlled Substances Act scheduled both psilocybin and psilocin in Schedule I, where it remains today. It was not until nearly three decades later that psilocybin was reexamined for its efficacy in several mental illnesses and substance use disorders. With stricter guidelines, safer regulations, and technological advancements, we see a renaissance of psilocybin research and psilocybin-assisted therapies that exhibit safety and efficacy. Recreational psilocybin use is briefly examined with an emphasis on set and setting, a critical component to hallucinogenic experiences. This comprehensive literature review acknowledges both the Indigenous and modern-day contexts of psilocybin. In addition, participant diversity and psychedelic experiences in historically marginalized racial and ethnic communities are explored. More in-depth research on psilocybin is required, but current studies provide preliminary evidence that psilocybin is misscheduled due to its healing properties for patients with multiple forms of depression, near-death anxiety, obsessive-compulsive disorder (OCD), substance use disorders, and addictions. In the recreational setting, on the other hand, life-changing increases in mindfulness and spirituality are commonly reported. Finally, the lack of racial and ethnic diversity among participants in emerging data is acknowledged, with solutions to this issue advocated for.

INTRODUCTION

As of 2021, over one in five adults in the United States experience mental illness (National Institute of Mental Health [NIMH], 2023) and

approximately 15% of adults suffer from a substance use disorder. However, nearly 94% of adults who need treatment for their disorder did not receive treatment (Mental Health America [MHA], 2022). In light of the COVID-19 pandemic, the demand for mental health and addiction disorder treatments has dramatically increased, particularly trauma, stressor, and substance-use related disorders (American Psychology Association [APA], 2022). The demand for treatment evidently outweighs the supply, with approximately three hundred and fifty patients regularly being assigned to one mental health provider (MHA, 2022) and nearly half of the surveyed psychologists who work with substance disorders reporting an inability to meet the demand (APA, 2022). Additionally, "despite federal and state investments made into mental healthcare, there has been an alarming increase in overdose and suicide rates" (Gorman, 2022, p. 1). Evidently, the United States is in dire need of mental healthcare reform.

Hundreds of years before scientific interest in psychedelics, Indigenous cultures have utilized entheogens, such as psilocybin, in spiritual ceremonies (Gonzàlez-Mariscal & Sosa-Cortés, 2022). Since the late 1940s, utilizing psychedelic substances as a treatment for mental health and substance use disorders has piqued the curiosity of dozens of researchers. It did not take long before psychedelic drugs became a recreational trend, which ultimately became a large component of the 1960s counterculture. In the short amount of time psychedelics were initially experimented with, the National Institutes of Health funded over one hundred and thirty grants (Nutt, 2019) to gather papers and data surrounding the use of psychedelics (including psilocybin) in clinical populations with "non-psychotic" mental illnesses (Rucker et al., 2018).

During the Nixon administration, the Controlled Substances Act of 1970 was a federal drug policy that organized a multitude of drugs into "schedules," ranging from Schedule I to Schedule V. The schedules served as categories ranging in the potential for abuse, the potential for dependence, and accepted medical use (U. S. Department of Justice, 2022). Both psilocybin and psilocin, two of the main components in the hallucinogenic mushrooms, were scheduled as Schedule I Drugs, which means that they have "a high potential for abuse," "no currently accepted medical use," and "lack of safety for use under medical supervision" (U. S. Department of Justice, 2022). The Controlled Substances Act was followed by The War on Drugs of 1971, which was strongly reinforced during Ronald Regan's presidency in 1981 (The Editors of Encyclopedia, 2023). Due to its scheduled category, research conducted on psilocybin was placed on a nearly three-decade hiatus before its resurgence in the

late 90s (Carhart-Harris & Goodwin, 2017), which we still see today alongside the mental health crisis (Kuntz, 2022). Current research studies continue to support the preliminary findings of the healing properties of psilocybin for mental health and substance use disorders, which would serve as a compelling option in combating the mental health crisis.

LITERATURE REVIEW

Teonanácatl

As the field of psychedelic science develops, it is imperative that its roots are fully acknowledged and respected. Before the introduction of psychedelics and their peculiar effects within modern science and society, Indigenous peoples worldwide would use entheogens in religious and spiritual ceremonies. Entheogen, meaning "creating the divine within" (Goldpaugh, 2021, p. 314), differs from psychedelics, meaning "mind manifesting" or "soul revealing" (Rucker et al., 2018, p. 201). In context, St. Arrnaud and Sharpe (2023) define entheogen as "any psychoactive substance used to evoke an altered state of consciousness interpreted as having religious or spiritual significance" (p. 69). Entheogens are not limited to psychedelics either, as cannabis and other natural grown plants have been used in religious and spiritual contexts (Ferrara, 2021). Psilocybin, a hallucinogenic mushroom, has strong roots stemming from the Indigenous populations of Central America and México. Traces were found amongst the Mazatec, Zapotec, Cuicatec, and Mixe peoples (Fagetti & Mercadillo, 2022). Evidence shows that this entheogen was used to attain wisdom and communicate with deities, as it was believed the mushrooms were associated with Xōchipilli, who is "the young god of dawn, flowers, life, fertility, and a patron of cacao" (Mathiowetz, 2018, p. 289). Referred to as teonanácatl ("Sacred Mushroom" in Nahuatl) by Aztec communities (Metzner, 2005, p. 1), its ancient use for healing was outlawed during the Spanish conquest of México due to its "satanic" nature going against Catholic morals and beliefs (Smith, 2016, p. 298). Additionally, the translation for teonanácatl was changed during conquest times into "God's Flesh" to further argue the supposed connection between devil worship and the sacred mushroom rituals (Metzner, 2005, p. 1), with the "God's Flesh" "translation" commonly used today. Despite attempts to destroy evidence and records of teonanácatl by the colonizers, Fray Bernardino de Sahagún wrote about teonanácatl and recounted its use in Historia de las Cosas de Nueva España in the 16th century (Carod-Artal, 2015,

p. 45). Hundreds of years later, in 1955, Robert Gordon Wasson's (1898-1986) and his wife Valentina Pavlovna Wasson (1901-1958) sought out Huautla de Jiménez, Oaxaca, México in search of the magic mushroom.

Velada con Niños Santos

Mazatec curandera (female healer or medicine woman) María Sabina (1894-1985) was initially reluctant to lead a velada (ceremony) for Wasson, as she only guided individuals who suffered from illness and not for reasons to "seek God" (Kabil, 2017). Obeying the words of her trustee, María agreed to allow Wasson to experience the velada with her niños santos, or holy children, as she called them (Schwartz-Marin et al., 2021). The experience was documented and photographed by Wasson and his colleagues which made its way to Life magazine in 1957, titled "Seeking the Magic Mushroom." Due to its intriguing content, as well as the buildup of the psychedelic era with recreational lysergic-acid diethylamide (LSD-25) use, the article boomed in popularity and made Huautla de Jiménez a tourist attraction. While Wasson initially used the alias "Eva Mendez" for María, he eventually revealed her identity and brought her unwanted attention and fame. María led veladas for most individuals who sought it but also felt the true properties of the niños santos were not valued, stating: "I realized the young people with long hair didn't need me to eat the little things. Kids ate them anywhere and anytime, and they didn't respect our customs" (Kabil, 2017). While Wasson reaped the benefits of introducing psilocybin to the US, María Sabina was left with unforeseen consequences: constant raids by authorities, the burning of her home, the murder of her son, and ostracization from her community (Stephen, 2020). Unfortunately, she passed away while in deep poverty but today, she is remembered as a sacred figure to the psychedelic movement (Stephen, 2020).

Early Experimentation

Shortly after the publication of "Seeking the Magic Mushroom," Albert Hoffman (1906-2008), the Swiss chemist who synthesized (1938) and ingested (1943) LSD-25, synthesized the hallucinogenic components of the magic mushroom (Nutt, 2019). In doing so, he labeled it "Indocybin" and marketed the pills for "therapeutic tranquilization" (Gerber et al., 2021). Pharmaceutical company Sandoz distributed both "Delysid" (LSD-25) and "Indocin" to psychiatrists for experimentation on patients (Nutt & Castle, 2023, p. 4). While both products were on the market, Delysid gained much more attention and experimentation at the time (Raison et al., 2022). Busch and Johnson, in 1950, published one of the first

studies of LSD-25 for patients with schizophrenia. Patients were shown to have worsened symptoms as a result of the psychedelic experience with no clinical improvement (Rucker et al., 2018). While early experimentation was not nearly as ethical as it is now, it established patient eligibility and participation in psychedelic research. Indeed, pre-existing or pre-dispositions to "psychotic" mental health conditions are an excluding factor in modern-day studies. Additionally, studies from the 1950s and 1960s did not consider the consequential role of set and setting for their patients, contributing to the "erratic outcomes" that we see significantly less of today within the therapeutic setting (Johnson et al., 2018, p. 153). Coined by Harvard Psilocybin Project co-founder Timothy Leary (1920-1996) in the 1960s, "set and setting" emphasizes the importance of both internal and external factors in regard to responding to psychedelic substances. "Set" includes the internal factors of intention, preparation, and state of mind, whereas "setting" is the physical and social environment where the substance is being taken (Hartogsohn, 2016). Set and setting seem to be key components to the experience and outcome of one's psychedelic trip, as there appear to be differences in experiences depending on recreational or therapeutic settings.

Federal Criminalization

With the knowledge of worsened symptoms in patients with schizophrenia, experimentation shifted towards those diagnosed with suffering from mental and substance use disorders before psychedelics became recreationally used in the counterculture of the 1960s (Rucker et al., 2018). As a result of the Controlled Substances Act of 1970, psilocybin and psilocin were ultimately scheduled as Schedule I substances despite the therapeutic potential early experimentation indicated (Carhart-Harris & Goodwin, 2017). The War on Drugs has failed in its "intended" mission - along with an increase in racially motivated murders, criminalization, and profiling (Earp et al., 2021), it has made clinical treatment and research difficult and costly while making recreational psychedelics easier to access (Eischens, 2019). Throughout the years, both researchers and volunteers have faced hurdles in therapeutic psilocybin trials (Ruoff, 2022). Luckily, federal restriction did not stop the interest and research entirely, with experimentation resuming in the 1990s to today.

DEA and FDA Research Process

With psilocybin being federally illegal as a Schedule I substance, researchers are required to obtain approval from the Federal Drug En-

forcement Agency, otherwise known as the DEA (Callahan et al., 2020). Fortunately, in 2018, the DEA announced they would "streamline the application process for researchers" (para. 1), making improvements on security and timeliness (Drug Enforcement Agency [DEA], 2018). Researchers must first register with the DEA and provide relevant information to the application, such as study protocol and researcher qualifications. In conjunction with DEA approval, psilocybin researchers must submit an Investigational New Drug (IND) application.

After getting approval for the IND, research proceeds in phases. The Federal Drug Administration (FDA) identifies phase one uses a small group of healthy human volunteers or individuals diagnosed with the target disease/condition and focuses on the safety and dosage of the substance (Commissioner, 2018). After several months, and with the approval to move forward, phase two expands up to several hundred participants who are diagnosed with the target disease/condition (Commissioner, 2018). The purpose of this phase is to evaluate the efficacy and side effects for anywhere from several months to two years (Commissioner, 2018). With phase two, the focus is sometimes split into 2a and 2b, with 2a monitoring dosages and 2b studying efficacy (NRC Research Institute, n.d.). While phase two is not considered large enough to demonstrate the benefits of the substance, it allows for the accumulation of more safety data (Commissioner, 2018). While 70% of drugs move from phase one to phase two, only 33% of drugs make it from phase two to phase three Commissioner, 2018). With the expansion of eligible participants going from several hundred up to three thousand, phase three (or the pivotal trial) aims to provide additional safety data by monitoring long-term or potentially rare side effects (Commissioner, 2018). Phase three lasts one to four years, with 25 to 30% of drugs moving onto the final phase after new drug application (NDA) approval (Commissioner, 2018). While there are no current psilocybin trials in the final phase of FDA clinical research, there are several in phases one, two, and even three. In regard to mental health, the FDA has given breakthrough therapy designations to two organizations for psilocybin therapy in individuals diagnosed with two types of depression: Compass Pathways (2018) for treatment-resistant depression (TRD) and Usona Institute for clinical depression (Business Wire, 2019). According to the Center for Drug Evaluation and Research (CDER, 2022), breakthrough therapy designations are "intended to expedite the development and review of drugs for serious or life-threatening conditions" (CDER, 2022) while meeting the requirement of "preliminary clinical evidence that demonstrates the drug

may have substantial improvement on at least one clinically significant endpoint over available therapy" (CDER, 2022).

FDA Breakthrough Therapy Studies

Compass Pathways (2022), a mental healthcare company based in Europe and North America, published a phase one trial of COMP360 in the Journal of Psychopharmacology. COMP360 is described as a "proprietary pharmaceutical-grade synthetic psilocybin formulation that has been optimized for stability and purity" (Rucker et al., 2022, p. 116). Completed in 2019, this randomized, placebo-controlled trial studied the short-term cognitive and emotional functions of eighty-nine healthy participants with a focus on safety (Rucker et al., 2022). With nearly ninety participants, COMPASS Pathways conducted the largest randomized controlled trial of psilocybin at that point in time (Rucker et al., 2022). Participants received a simultaneous single oral dose of either 10mg, 25mg, or a placebo. Additionally, participants were given one-on-one psychological support by having an assigned therapist available throughout the session. Rucker and colleagues kept track of treatment emergent-adverse events and severe treatment emergent-adverse events, or TEAEs. For the purposes of this study, treatment emergent-adverse events were defined as "any AEs (adverse events) with an onset on or after the dose of study drug, or any pre-existing condition that worsened on or after the dose of study drug" (Rucker et al., 2022, p. 117). This study reported five-hundred and eleven TEAEs within the twelve-week follow-up timeframe, with 67% starting and resolving on the day of administration. Furthermore, over 90% of reported adverse events resolved on the day of administration correlate to symptoms of psilocybin ingestion, including hallucination, illusion, and mood alteration (Rucker et al., 2022). With mood alteration, over 95% of reports were positive or neutral in change (Rucker et al., 2022). This study concluded that the single doses of both 10mg and 25mg did not cause serious adverse events or short and long-term effects and were generally well tolerated (Rucker et al., 2022).

Usona Institute, based in Wisconsin, launched a phase two trial shortly following the designation (Business Wire, 2019). One hundred participants were gathered for "the first Phase 2, randomized, double-blind, placebo-controlled study of single-dose psilocybin to treat major depressive disorder." (Usona Institute, 2023, para. 1). The study measures the efficacy between a single 25mg dose of psilocybin and a single 100mg dose of Niacin (vitamin B3), which was the active placebo selected for this study (CDER, 2022). The primary outcome measure

for this study focuses on changes in the Montgomery-Asberg Depression Rating Scale (MADRS), which measures depression severity and discerns changes in post-antidepressant treatment (CDER, 2022). This scale was used from baseline throughout follow-ups for about two months (CDER, 2022). While the results of Usona Institute's study have yet to be published, it makes history as the first of its kind.

Present-Day Experimentation: Treatment Resistant Depression

Watts et al. (2017) published a study recounting patients' experiences after psilocybin treatment for treatment resistant depression, or TRD. Twenty participants orally ingested two different psilocybin doses (10mg and 25mg) on separate occasions while continuously being monitored and guided by mental healthcare professionals. Participants are guided to "let go" and surrender to the psychedelic experience (Watts et al., 2017), as resistance has been linked to negative experiences (Gandy, 2022). A semi-structured interview process gathered the consensually reported experiences of nineteen out of twenty participants, which focused on pre- and post-treatment depression and the ways in which the psilocybin treatment compares to other treatments. Watts et. al (2017) noticed commonalities among participant responses, such as feelings of disconnect in the state of their depression and a history of avoiding and/or repressing feelings, memories, and thoughts that invoked pain. Furthermore, participants described their feelings of disconnect, avoidance, and/or repression mirrored in previous treatments (Watts et al., 2017). When comparing these three commonalities to the psilocybin-induced sessions, patients reported the feeling of disconnect being profoundly rectified and confronted with their previous pain, ultimately leading to acceptance. In regard to conventional treatments for TRD and the therapeutic psilocybin experience, participants felt the psilocybin experience was opposite to previous treatments, promoting acceptance and reconnection (Watts et al., 2017). These reported experiences held true within the next weeks and months post-treatment, seemingly influencing participants in profound ways. Participants report picking up/revisiting healthy hobbies, connecting with loved ones and strangers, and discovering a new perspective. Some patients also reported their experiences with antidepression medications as "debilitating" and came with severe withdrawal symptoms while simply masking the underlying problems (Watts et al., 2017). While some participants report the return of their symptoms at follow-up, Watts et. al (2017) recorded reports of improvement in their sense of purpose and hope.

Present-Day Experimentation: Obsessive Compulsive Disorder

While there are a number of study publications on psilocybin therapy for individuals diagnosed with depression, there is a comparatively lacking amount done with people living with obsessive-compulsive disorder (OCD). Kelmendi and colleagues (2022) assessed the efficacy of single-dose psilocybin treatment in a double-blind, placebo-controlled, and randomized study in patients with treatment-resistant OCD. While most participants either demonstrated improvement or no significant change, Kelmendi et al. (2022) make note of one patient, Daniel, who demonstrated substantial and sustained benefits from the trial. This particular participant was diagnosed with OCD around ten years of age while reporting symptoms in his early teens. He had previous recreational experiences with psychedelic substances (specifically psilocybin and LSD-25) and reported transient benefits if they were to occur. Kelmendi et al. (2022) provided Daniel with an oral dosage of 0.25 mg/kg, or 19.4 mg. While Daniel was initially resistant to the peak of his altered state of consciousness, he let go and allowed himself to experience a transformative death and rebirth (Kelmendi et al., 2022). During the follow-up integration sessions, Daniel would highlight the momentous insights he gained through this experience. So much so, in fact, that at his twelve-month post-dose follow-up, he reported OCD no longer having consequential effects on his life. When Daniel was contacted for an additional one-year follow-up, he continued to be "OCD-free" (Kelmendi et al., 2022). At the time of the twelve-week and one-year follow-ups, Daniel reports experiencing stressful life events that briefly returned significant OCD symptoms. However, unlike pre-dose coping, Daniel allowed himself to feel and process his emotions related to the event. In addition, he applied teachings from the study, including preparation/integration sessions and the psychedelic experience itself. After about two weeks of active and intentional effort, Daniel's OCD "faded" (Kelmendi et al., 2022).

Present-Day Experimentation: Near-Death Anxiety

With researched mystical and spiritual effects, combined with a changed perspective, psilocybin experimentation gained findings for the ways in which psilocybin impacts near-death anxiety in patients with chronic illnesses. Agin-Liebes et al. (2020) of New York University's School of Medicine investigated the efficacy of a single dose of 0.3 mg psilocybin in alleviating existential and psychiatric distress for patients with life-threatening cancer. This experimentation was compared to a 250 mg of niacin placebo. Three primary measures were used for

the purpose of collecting data on anxiety and depression, with secondary measures analyzing the quality of life, spirituality, mystical experience, existential distress, and persisting effects of psilocybin (Agin-Liebs et al., 2020). One short-term follow-up (6.5 to 8 months) and two long-term follow-ups (LTFU) of several years post-treatment sought out to compare the efficacy and consistency of the experience, with the first one being 3.2 years and the second one being 4.5 years (Agin-Liebs et al., 2020). The researchers found that results suggest that a single dose of psilocybin is associated with the reductions of death anxiety, depression, hopelessness, and demoralization up to an average of the second LTFU of 4.5 years. Statistically, 60% to 80% of participants "met criteria for clinically significant antidepressant or anxiolytic responses" (Agin-Liebs et al., 2020, para. 3), and nearly two-thirds to 100% "attributed positive life changes to the psilocybin-assisted therapy experience and rated it among the most personally meaningful and spiritually significant experiences of their lives" (Agin-Liebs et al., 2020, para. 3).

Present-Day Experimentation: Substance Use Disorder

Other areas of pre- and post-War on Drugs data collected for psilocybin-assisted therapy include the chronic diseases of substance use disorders (SUDs) and addictions. On the surface, it may seem counterintuitive to use a Schedule I substance as a therapy for individuals with SUDs and addictions. However, studies show that psilocybin has a much lower potential for physical dependency, toxicity, and addiction, especially when compared to modern-day addiction medications and other illegal drugs with healing properties in small amounts (Johnson et al., 2018). While modern pharmaceutical medications to treat SUDs are revolutionary, there is an evident necessity for improvement. According to Johnson (2018):

The state of addiction medicine is likewise disappointing. For many, but not all substances of addiction, approved medications are available that perform better than a placebo. Even with these important medications, relapse rates are substantial and in dire need of improvement. (p. 286)

Johnson and colleagues (2017) at John Hopkins University School of Medicine examined the long-term effects of psilocybin with cognitive behavioral therapy (CBT) in fifteen participants with tobacco dependence. The open-label pilot study administered one moderate (20mg) dose at week five and one high (30mg) dose at week seven, with an optional third 30mg dosage during week thirteen (Johnson et al., 2017).

Each participant completed the twelve-month follow-up while twelve of fifteen participated in the long-term follow-up. At the twelve-month follow-up, Johnson et al. (2017) found ten of fifteen participants to be abstinent from smoking. At the long-term follow-up, three-fourths of the twelve were abstinent from smoking. Along with the reported abstinence at the twelve-month follow-up, over 85% of participants found the psilocybin experience to be "among the top five most personally meaningful and spiritually significant experiences of their lives" (Johnson et al., 2017, p. 1). Johnson and colleagues found that psilocybin doses, along with CBT, had evidently higher abstinence rates (six months) in comparison to other therapeutic and medicinal methods (Johnson et al., 2017).

Bogenschutz and colleagues (2022) recruited 95 volunteers diagnosed with alcohol dependence in New Mexico and New York for a double-blind trial observing drinking outcomes after psilocybin-assisted therapy compared to an active placebo. This study administered 25 mg/70 kg of psilocybin vs 50mg of diphenhydramine (commonly known as Benadryl) during the first dosage session. During the second dosage session, participants received 25 mg to 40 mg/70 kg of psilocybin vs 50 mg to 100 mg of diphenhydramine. Along with dosing, volunteers received CBT and motivational enhancement therapy (MET). Ninety-three of ninety-five participants received at least one dose of psilocybin. Bogenschutz et al. (2022) assessed the number of heavy drinking days throughout thirty-two weeks following initial administration. As a result, heavy drinking days were 9.7% in the psilocybin group whereas the diphenhydramine group reported 23.6%, making a mean difference of 13.9% (p. 953). Moreover, drinks per day were lower in the psilocybin group than in the diphenhydramine group (Bogenschutz et al., 2022).

Neuroscience of Mindfulness

As stated throughout handfuls of studies, mindfulness is often associated and reported with post-psychedelic experiences. Madsen et al. (2020) observed positron emission tomography (PET) neuroimaging and assessed mindfulness scores through a questionnaire in ten healthy yet psychedelic-naïve participants. For the purposes of this study, and with its roots in Buddhism (Baer, 2019), mindfulness was "defined as nonjudgmental awareness of the present moment, which provides an opportunity to acknowledge and accept difficult physical and emotional sensations" (Hosey et al., 2018, para. 1). Madsen et al. (2020) found that a significant increase in mindfulness was sustained at the three-month follow-up, with neuroimages supporting the relationship between psilo-

cybin and the serotonergic 5-HT2A receptor. Psychedelics are agonists, which means they bind to neurotransmitter receptors - the 5HT2A receptors, in this case. Stoliker et al. (2022) observed changes in neuromodulatory functioning - specifically in the strength of communication between neurons, or synaptic efficacy (Lines et al., 2017). Four main neuromodulatory systems include norepinephrine, acetylcholine, dopamine, and serotonin (Slater et al., 2022). Because of the agonism of the 5-HT2A receptors, Stoliker et al. (2022) argue that psychedelics "may have a particularly powerful effect on sentience and consciousness" (p. 877) and its potential for neural plasticity likely contributes to the therapeutic experience observed in modern-day studies.

Default Mode Network

Advancements in research and technology have allowed for a deeper understanding of neuroactivity while under the influence. Researchers have since monitored the activity between the default mode network (DMN) and psychedelics. The DMN is the "grouping of interconnected brain regions characterized by increased temporal coherence at rest…" (Gattuso et al., 2023, p. 3). Essentially, the DMN is most active during resting states (less focused on cognitively intense tasks) and associated with "self-referencing, mind wandering and autobiographical memories" (Gattuso et al., 2023, p. 3). While overactive DMN activity has shown a correlation with mental illnesses and their symptoms (overthinking and negative thought patterns, for example), decreased activity of DMN is somewhat specific to psychedelics, differentiating them from selective serotonin reuptake inhibitors, or SSRIs (Gattuso et al., 2023). With the decrease of DMN activity that psychedelics accomplish, other brain activity is promoted to increase. Furthermore, with disruption in self-reflection and mind wandering, participants may "shift perspectives and overcome maladaptive thought patterns associated with mental illness" (Marks, 2020, p. 661). While it is unclear if the decrease in DMN activity is the cause of the long-lasting therapeutic benefit that psychedelics seem to portray, there is an evident connection that makes it a leading theory among researchers (Marks, 2020).

Microdosing

Along with modern-day studies, the trend of microdosing has gained recreational popularity among the general public (Cavanna et al., 2022). In this case, microdosing is defined as routinely self-administering a low sub-perceptual dose of psilocybin, where the dosage is low

enough to avoid an altered state of consciousness while still reaping some of the benefits. Macrodosing, on the other hand, is taking large enough doses to experience transcendence and an altered state of consciousness. With studies mainly focused on macrodoses, little is known about microdosing from a scientific perspective. Microdosing typically consists of taking one-tenth to one-twentieth of a macrodose every three to four days (Kaypak et al., 2022). Like macrodosing, microdosing also has an Indigenous history in things such as aiding symptoms of illness, libido, and courage (Kaypak et al., 2022). Self-reported data often mentions an array of microdosing benefits such as increased and improved sociability, wisdom, cognition, and creativity (Kaypak et al., 2022). However, clinical trial findings on microdosing are not as clear and consistent with its conclusions as macrodosing is. Cavanna et al. (2022) held a double-blind placebo-controlled study for thirty-four participants and did not find 0.5g of psilocybin to impact creativity, physical activity, and cognition significantly. Still, they did find "impaired performances" during certain cognitive tasks. Cavanna et al. (2022) raised concerns about potential confirmation bias and the placebo effect, especially due to the consistency of breaking blind.

Serious Adverse Events and Side Effects

Both microdoses and macrodoses come with their reported side effects. Serious adverse events (SAEs), defined as things such as hospitalization and permanent damage, are extremely rare in clinical research trials. Kopra et al. (2022) analyzed the data from the Global Drug Survey of 2017, focusing on the 9,233 self-reported psilocybin users within that past year. Of the over nine-thousand users, only nineteen reported seeking out emergency medical treatment with all but one returning back to normalcy within twenty-four hours. From this analysis, it was found that there was only one predictor associated with a higher risk of emergency medical intervention: young age (Kopra et al., 2022). The reason for emergency medical treatment was largely reported to be due to substance mixing and poor set and setting (Kopra et al., 2022).

While set and setting play a critical role in the outcome of the psychedelic experience, there are drug-induced side effects that typically occur regardless. These drug-induced side effects are generally within the classifications of emotional, perceptual, cognitive, and ego dissolution (Kargbo, 2020). The intensity of side effects, as well as some side effects in general, such as ego dissolution, are dose-dependent regardless of which combination of side effects are experienced. According to Karg-

bo (2020), emotional side effects may consist of the intensification and broadening of feelings and emotions which may include interconnectedness and euphoria. Kargbo (2020) emphasizes that emotions are largely influenced by social and environmental stimuli, so supportive contexts are much more likely to generate positive feelings and emotions. Perceptual side effects may include visual distortions, hallucinations, and mental imagery (Kargbo, 2020). In addition, perceptions of time and location may lose their linear relationship during the experience. Kargbo (2020) describes cognitive side effects as "enigmatic." However, traits associated with creativity, such as associating meaning with musical stimuli and lateral thinking, may increase. Finally, modest to profound feelings of ego dissolution may occur. Ego dissolution, also referred to as "ego death," is described as the loss of a sense of self-identity and persona. While this sounds alarming, it appears to be one of the most therapeutic aspects of psilocybin-guided experiences that set it apart from anything else experienced by participants. Naturally, ego dissolution commonly replaces the sense of "me" with a sense of "we," with "we" referring to the interconnectedness of self with the universe. Experiences from ego dissolution, like other symptoms, are reliant on set and setting.

Through neuroimaging technology, Mason et al. (2020) observed the region-dependent adjustments in glutamate following a 0.17 mg/kg dose of psilocybin and the ways in which it may correlate with the predictive outcome of negative and positive ego-dissolution experiences. While increased levels of medial prefrontal cortical glutamate had associations with negative ego-dissolution experiences, decreased levels of hippocampal glutamate had associations with positive ego-dissolution experiences (Mason et al., 2020). In terms of other negative experiences, there are small chances that a psychedelic experience can trigger hallucinogen persisting perception disorder, or HPPD.

Hallucinogen Persisting Perception Disorder

Recognized as a diagnosable disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) and International Classification of Diseases, Eleventh Revision (ICD-11), HPPD is categorized by the reexperiencing of symptoms associated with the substance after its use, with "clinically meaningful impairment and/or suffering are required for its diagnosis" (Halpern et al., 2016, p. 334). Two subtypes of HPPD have been categorized as HPPD I and HPPD II. HPPD I, recreationally recognized as "flashbacks," consists of unprovoked, short-lived, reexperienced symptoms of an altered state anywhere

from days to years prior, which may include reminiscent perceptual and/or emotional changes (Halpern et al., 2016). Halpern et al. (2016) note that symptoms are commonly visual alterations, including a heightened intensity in the vibrancy and intensity of colors, though perceptions of time and ego may be shifted in rarer cases. ICD-10 distinguishes HPPD I from psychosis in that "Flashbacks may be distinguished from psychotic disorders partly by their episodic nature, frequently of very short duration (seconds or minutes), and by their duplication (sometimes exact) of previous drug-related experiences…they are usually self-limited and diminish in duration, intensity and frequency with time." (Halpern et al., 2016, p. 336). HPPD II, on the other hand, are more frequent and prolonged visual alterations. Visual snow (grainy vision, similar to that of static), halos (glow surrounding objects and/or people), trails (afterimage following a moving object), and palinopsia (reoccurrence of the image of an object after being removed from view) may be included. While the exact number of cases is unknown, the DSM-V estimates that 4.2% of hallucinogen users "experience HPPD-like symptoms" (Vis et al., 2021).

HPPD is not strictly associated with psychedelics, as Halpern et al. (2016) found HPPD has also been reportedly experienced following benzodiazepine, amphetamine, inhalant, cannabis, and alcohol use. Furthermore, Halpern et al. (2016) state that, in clinical settings, HPPD is rarely encountered, further supporting the significance of set and setting - something psilocybin-assisted therapy ensures the quality of.

Structure of Psilocybin-Assisted Psychotherapy

According to Brennan and Belser (2022), current models of psilocybin-assisted psychotherapy (PAP) include preparation, administration, and integration sessions. Following the paperwork and screening process to determine eligibility, at least one preparation session is conducted with the intention of preparing participants for the administration phase. The preparation session(s) serves as an opportunity to educate recipients on what to expect during the administration phase. In addition, a therapeutic relationship is established to ensure the client feels safe and supported (Horton et al., 2021) and goals/intentions are set.

The administration phase is when the dosage of psilocybin is ingested in the care and supervision of two therapists, often a female-male dyad or two therapists of the same gender identity as the recipient to ensure comfortability (Horton et al., 2021). In a comparison of eleven PAP studies, Horton et al. (2021) observed that, while there is a difference in length and frequency, each study instructed its participants to position

themselves in a lying position, wear eyeshades, and listen to a playlist of music for a greater part of the session(s). The addition of music to a psychedelic experience has been found to be pivotal to the therapeutic outcome during early psychedelic research trials (Horton et al., 2021). Participants throughout multiple modern-day studies have highlighted the importance of music during their experience, some of which describe its role in experiencing and accepting difficult emotions (Horton et al., 2021). Most of the studies analyzed by Horton et al. (2021) described the setting in which the administration phase took place, all of which had the intention of promoting comfortability and resembled a living room as opposed to a laboratory. Administration sessions focus on the goal/intention of the client and take on a nondirective approach (Horton et al., 2021). Also referred to as person-centered and transpersonal therapy (Yao & Kabir, 2023), a nondirective approach consists of a client-led exploration of conversation, topics, and answers, and is centered around the core beliefs of congruence, empathy, and unconditional positive regard (Yao & Kabir, 2023).

Finally, integration sessions involve the discussion of the client's experience during and after the administration session. Horton et al. (2021) found that a variety of modalities of posttreatment techniques are utilized depending on the study, such as journaling, cognitive-behavioral therapy, motivational enhancement therapy, etc. In addition, a combination of different psychological outcome measures is used depending on the psychological and medical background of clients, such as the Beck Depression Inventory, Timeline Followback, etc. In conjunction with these outcome measures used in a variety of settings, there are specific outcome measures used within the realm of psychedelic-assisted therapy, such as the commonly utilized Mystical Experience Questionnaire (MEQ), measuring mystical, positive mood, transcendence of time and space and ineffability (Ko et al., 2022, para. 21). Session patterns have not been the only thing noted within the field of psilocybin-assisted therapy. Indeed, it has also been acknowledged that there appears to be a historical and current lack of diversity within participants.

DISCUSSION

Evident Disparities in Representation

It is critical to acknowledge the consequences of Gordon Wasson's betrayal against María Sabina and the overall Mexican Indigenous com-

munity. From the perspective of Indigenous peoples, the story of Gordon Wasson is one of colonization and cultural appropriation (Gerber et al., 2021). However, despite the rich history of the Indigenous roots of psilocybin and veladas, and regardless of the disproportionate levels of poor mental health within vulnerable populations (Michaels et al., 2018), marginalized communities are substantially less represented amongst modern-day psilocybin-assisted therapies and research trials. While the US National Institute of Health (NIH) issued a mandate for funded research to include participants of color and methods for reaching diverse populations to be included in proposals in 1993, Michaels et al. (2018) found that, across 18 worldwide psychedelic experiments between 2000 to 2018, 232 out of 282 participants (82.3%) identified as non-Hispanic White.

Moreover, of all the research studies mentioned in the literature review, those that mentioned racial and ethnic demographics all had a White majority. A study by Agin-Liebes et al. (2020) on psilocybin and existential distress in terminally ill patients presented the highest White majority with 14 out of 15 (93%) White participants and one Asian participant. With patents developing, Gerber et al. (2021) noted that, at the time of publication, none of the pharmaceutical developers of twenty-four registered patent processes "have reached any legitimate or reciprocal agreements with the Mazatecs, or any other indigenous communities" (p. 576). It is evident that historically marginalized communities are not participating in or having a say in the development of psilocybin in psychiatry, dangerously treading on the risk of whitewashing (Thrul & Garcia-Romeu, 2021). Unfortunately, there are extremely limited studies that explore the efficacy of psilocybin with BIPOC-specific concerns and experiences.

Psilocybin Experiences of People of Color

Williams and colleagues launched an observational and cross-sectional virtual survey in 2019 to recruit responses on BIPOC's experiences with racial trauma and recreational psychedelic use consisting of psilocybin (37%), LSD-25 (36%), and 3, 4-Methylenedioxy-methamphetamine (MDMA, 27%) (Williams et al., 2020). Of three hundred and thirteen participants, the two largest racial demographics were of Black/African heritage (32%) and East Asian, South Asian, Asian American/Canadian (29%) with 19% identifying as Hispanic (Williams et al., 2020). Measures of depression, anxiety, stress, and racial trauma before and after the psychedelic experience were collected and compared, with all reported levels decreasing after the psychedelic experience (Williams et al., 2020). Provided the difference in manifestations and clinical presentations of

psychological symptoms amongst people of color (Michaels et al., 2018), as well as the general difference in lived experiences, studies that examine experiences of people of color are a critical factor in effectively and inclusively moving forward.

Potential Solutions

Michaels et al. (2018) mention several suggestions for cultural, racial, and ethnic inclusion, such as diverse environments, music, and artwork to maximize comfort. Moreover, Michaels et al. (2018) suggest culturally inclusive language and "ethnoracially-matched" researchers to build a stronger therapeutic alliance, as well as compensation to address economic concerns. Some suggestions made by Ortiz et al. (2022) include the development of multilingual self-report measures and encourage the acknowledgment of religious interpretations of psilocybin experiences given the significance of religion within a multitude of underrepresented cultures. Ortiz et al. (2022) also makes note of the potential feeling of powerlessness amongst various vulnerable populations and suggests engaging "participants as equal partners with full agency" (p. 2) and discusses the relationship between preoccupation and surrender to the psychedelic experience and outcome depending on therapeutic alliance. Finally, Ortiz et al. (2022) emphasizes the importance of transparency in comprehensible language. Notably, these suggestions are both doable and overdue. Given that the field focuses on client comfort, it's only logical to implement intentional and genuine cultural humility to encourage and sustain participation from underrepresented communities for the betterment of the mental health crisis as a whole.

CONCLUSION

While decades of U.S. research have been lost following twenty years after the Controlled Substances Act of 1970 went into effect, initial and modern-day studies show preliminary evidence of safety and competence within healthy individuals and populations diagnosed with different psychiatric and medical conditions. More general studies are necessary to definitively provide the option of psilocybin-assisted therapy in psychiatry, but even more studies with larger underrepresented identities are urgent. Certainly, the overall research on psilocybin should not be discredited entirely. However, as psilocybin makes progress through its third clinical trial phase as of January 2023 through COMPASS Pathways (U.S. National Library of Medicine, 2023), acknowledging historical

roots, providing inclusive spaces, and practicing multicultural humility moving forward are detrimental to accurate data collection and efficacy in reaching and helping people of color. Future research will analyze mixed-method data from an anonymous, virtual, self-reported survey. In addition, further exploration of psilocybin in several contexts will be addressed as developments are made.

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