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Abstract

Microdosing with psilocybin, a psychoactive compound found in certain species of mushrooms, has gained popularity in recent years as a means of enhancing mood, cognition, and creativity without inducing the full-blown psychedelic experience. There are many potential benefits associated with microdosing with psilocybin. Although studies do show many positive effects of microdosing with psilocybin, long-term research is required to make a conclusive statement regarding this topic. Furthermore, there are risks and concerns involved that need to be considered, including the illegality of psilocybin and the lack of research. This paper will review the available literature on microdosing with psilocybin. It will explore the mechanism of action, potential benefits and effects of microdosing with psilocybin, as well as the risks and concerns associated with this practice. While research on psilocybin's effectiveness in treating certain mental disorders looks promising, it is yet to be determined whether microdoses of the substance produce similar effects.

Introduction

Psilocybe Cubensis and Copelandia are the most common species of psychedelic mushrooms. Psilocin and psilocybin, the active compounds, are found in varying amounts in these mushrooms. Psilocybe Cubensis has higher levels of psilocybin, while Copelandia has higher levels of psilocin. The psilocybin content ranges from 0.37% to 1.30% in Psilocybe Cubensis and from 0.08% to 0.22% in Copelandia. Psilocybe Semilanceata, a British species, contains only psilocybin, with concentrations ranging from 0.17% to 1.96%. The concentration of psilocybin can vary within and between species and depends on factors such as collection time, preservation, and growth conditions. Users reported that recreational doses depend on the species and individual experience (Kuypers et al., 2019).

Psilocybin has been used for centuries in various cultures, most notably by the Mazatec people of Mexico for traditional healing methods. In the 16th century, a Franciscan friar named Bernardino de Sahagun reported using mushrooms, 'Teonanacatl', for medicinal purposes. In his reports, he included that only two or three needed to be eaten to cure a fever or rheumatism. The low doses of psilocybin mentioned here induced visions, suggesting that the dosage is not what would be considered microdosing today (Kuypers et al., 2019). Towards the second half of the 20th century, the Western world began to use psilocybin and other psychedelics as part of the counterculture movement. The eventual criminalization of their use prevented research on these substances for subsequent decades (Nichols, 2016). The use of psilocybin in a clinical setting has seen a spike in interest recently, leading to an increase in studies on its clinical uses and benefits.

Methods

The data for this paper was collected through a comprehensive review of the literature available in various databases. A systematic search was conducted using databases such as ProQuest, PubMed, The Touro College Library online, EBSCO, and Google Scholar. The search strategy involved the use of relevant keywords and controlled vocabulary terms to identify relevant articles.

Effects of Psilocybin

Psilocybin has been shown to have many positive effects. Participants in a study conducted in 2020 reported improved quality of life after psilocybin use. Additionally, they reported overall healthier behaviors, enhanced connections with others, improvement in psychological well-being, positive changes in attitude and mood, and increased self-confidence. In a study done on long-term heavy cigarette smokers, after two psilocybin therapy sessions, 80% of the participants abstained from smoking for six months. Eight months following one or two psilocybin doses, the drinking habits of alcohol-addicted patients significantly decreased. Patients with treatment-resistant depression received 10-25 mg of psilocybin in two sessions. One week later, the patients reported a notable decrease in depressive symptoms. Furthermore, amongst end-stage cancer patients, there was a notable reduction in both anxiety and depression three months after a single dose of psilocybin (Alshaikhli et al., 2021). Another study found that psilocybin induced rapid and long-lasting antidepressant effects in mice (Hesselgrave et al., 2021).

Although psilocybin has many positive effects, many risks and concerns are involved (T. Anderson et al., 2019). Effects of psilocybin include visual alteration, frightening hallucinations, dizziness, distorted thinking, confusion, paranoia, lack of coordination, impaired concentration, drowsiness and yawning, muscle weakness, unusual body sensations, dilated pupils, and nausea and vomiting. Hallucinogen-persisting perception disorder (HPPD) is a condition where individuals who have used psilocybin may have long-lasting and distressing changes in their perception of the world. These changes often manifest as visual flashbacks, which involve re-experiencing intense and upsetting visual effects. Flashbacks can persist for weeks to even years after the use of the hallucinogen. Medical professionals now recognize HPPD as a diagnosed condition associated with hallucinogen use (Fnp, 2023). In some cases, individuals who use psilocybin may encounter adverse effects such as fear, agitation, confusion, delirium, psychosis, and symptoms that resemble schizophrenia. These effects can be severe and may necessitate seeking

medical assistance in the emergency room. There is also the risk of accidental ingestion of toxic mushrooms as there are many varieties of mushrooms that resemble psilocybin. Muscle spasms, delirium, and confusion are symptoms of mushroom poisoning.

Psilocybin is not considered chemically addictive since there are no physical withdrawal symptoms associated with its discontinuation. However, individuals who have been using psilocybin for several days may experience psychological withdrawal, finding it challenging to readjust to their common perception of reality. Additionally, frequent use of psilocybin can lead to the development of tolerance, whereby the desired effects of the drug diminish over time (Lowe et al., 2021). Cross-tolerance can occur between psilocybin and other drugs like LSD and mescaline, meaning that if tolerance develops to one of these substances, it may also affect the response to the others. Individuals who use these drugs simultaneously would need to allow several days between doses to prevent cross-tolerance. More importantly, tolerance can increase the risk of adverse reactions, as individuals may take larger doses than they can safely handle.

The impact of psilocybin varies among individuals, depending on their mental state, personality, and immediate environment. Those with existing mental health conditions or feelings of anxiety regarding psilocybin use are more prone to negative experiences. Psychological distress, such as severe anxiety or temporary psychosis, is frequently reported as an adverse effect after recreational psilocybin use (Fnp, 2023).

Mechanism of Action

Psilocin, the active compound in psilocybin mushrooms, primarily attaches to different serotonin receptors, including 5-HT1A, 5-HT1D, 5-HT1E, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT5, 5-HT6, and 5-HT7, as well as the serotonin and norepinephrine transporters, which is similar to the mechanism of (3,4-Methylenedioxymethamphetamine), commonly known as Ecstacy (tablet form) or Molly (crystal form). Psilocin can bind to all 5-HT receptors separately, except for 5-HT2B, which binds cooperatively. These 5-HT receptors are spread out throughout the brain and have an impact on various behavioral and neuropsychological effects that microdosing is claimed to create. Psilocin acts as a partial agonist on the 5-HT2A receptor and has a response of around 46% (+/-2.4) compared to serotonin's response in signaling through the phospholipase C (PLC) pathway (Kuypers et al., 2019).

Psilocybin has been shown to react with serotonin (5-hydroxytryptamine) type 2A (5-HT2A) receptors, causing hallucinogenic effects by inducing hyper-frontality resulting in antianxiety and antidepressant effects. One potential mechanism is the deactivation of hyperactivity of the medial prefrontal cortex (mPFC), which is hyperactive in depressed individuals. Psilocybin can also be effective as an antidepressant via modulation of the limbic regions, in addition to the prefrontal brain regions. An important limbic system component is the amygdala, which plays a key role in processing emotions; depression is often accompanied by muted responsiveness to emotional stimuli. Thus, modulation of the amygdala can have significant effects on depression modulation (Lowe et al., 2021).

The serotonin 5-HT2A receptors are present in several brain regions associated with psychotic symptoms, including the prefrontal cortex, striatum, ventral tegmental area, and thalamus. Within the ventral tegmental area, there are dopaminergic cell bodies that play a role in regulating emotions, cognitive behaviors, and the brain's reward system. While the precise neuropharmacological mechanisms of psilocybin are not fully understood, it is believed to interact with both the serotonergic and mesolimbic dopaminergic systems, which are involved in the brain's reward circuitry. This interaction with the mesolimbic pathway may contribute to the low potential for psilocybin to be abused. Furthermore, there is a potential link between depression and dopamine deficiency in the mesolimbic pathways, suggesting that the modulation of these pathways by psilocybin may have implications for treating depression (Lowe et al., 2021).

It is believed that schizophrenia, along with other mood and anxiety disorders, may be characterized by an imbalance or dysregulation of serotonin and dopamine levels. One study suggests that serotonergic receptors, specifically the 5-HT2A and 5-HT1A receptors, play a crucial role in regulating dopamine release in the striatum during acute psychoses. This suggests that psilocybin may hold promise in treating schizophrenia and other psychiatric disorders. In another study, psilocybin was indirectly responsible for increasing endogenous dopamine levels by reducing the binding potential of 11C-raclopride in the caudate nucleus (19%) and putamen (20%).

According to several studies, psilocybin has been found to bring about significant changes in brain activity and connections between different brain regions. These changes include the breaking down of connections between associative networks and the integration of sensory function networks, which may explain the subjective effects of psilocybin and a state of unconstrained cognition. It's been suggested that psilocybin's psychotomimetic effects may be due to interactions with feedback loops between the cortex and thalamus. Psilocybin administration also leads to general cortical activation, as seen through increased

levels of the cerebral metabolic rate of glucose in several brain regions, which is positively linked with "ego dissolution" hallucinations. Additionally, the myocardial metabolic rate of glucose (MRGlu) increased in specific regions of the right-hemispheric frontotemporal cortex (Lowe et al., 2021).

Psychedelics exert therapeutic effects for psychiatric disorders by acutely destabilizing local brain network hubs and global network connectivity via amplification of neuronal avalanches, providing the occasion for brain network "resetting" after the acute effects have resolved. Anti-inflammatory effects may hold promise for efficacy in the treatment of inflammation-related nonpsychiatric as well as potentially psychiatric disorders (Nichols et al., 2017).

A 2021 study was conducted to examine how psilocybin affects functional connectivity in mice across the entire brain region. One possible way that psilocybin may alleviate depression is through its interaction with or alteration of the default-mode network (DMN). Resting-state functional magnetic resonance imaging (fMRI) was used to demonstrate that psilocybin reduces functional connectivity within dopamine-associated striatal networks and increases connectivity between 5-HT-associated networks and cortical areas. This study confirms the interaction of psilocybin with the mesolimbic dopaminergic pathway to produce neural and psychological effects (Grandjean et al., 2021). Another study found that psilocin, an active metabolite of psilocybin, increases the concentrations of both extracellular dopamine and 5-HT in the mesoaccumbens and/or mesocortical pathway. This suggests that psilocybin may have another possible mechanism for treating depression by increasing dopamine, which regulates emotions and physical well-being. However, the concentrations of dopamine and 5-HT in the ventral tegmental area (VTA) were not affected, implying that other brain areas may influence the reward circuitry besides the VTA (Lowe et al., 2021).

While indoleamine LSD and other hallucinogens attach to dopamine D2 receptors and create dopaminergic "psychotic" experiences, psilocybin and psilocin do not have any affinity for dopamine D2 receptors, despite the functional interaction between the serotoninergic and central dopaminergic systems. This relationship has been confirmed by experiments with haloperidol, which is a D2 receptor antagonist that lessens the psychotomimetic effects of psilocybin (Lowe et al., 2021).

Psilocybin is known to activate 5-HT2A receptors (López-Giménez & González-Maeso, 2017), which then activate AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors, leading to increased levels of glutamate, a substance that helps maintain normal brain function. Additionally, psilocybin treatment, often combined with psychological support, has been found to enhance sensitivity to positive emotions in the right amygdala and reduce sensitivity to negative or neutral emotions. Psilocybin also has the potential to reduce the amygdala's response to threatening visual stimuli and decrease the amygdala's top-down modulation of the primary visual cortex (Lowe et al., 2021).

This differs from selective serotonin reuptake inhibitors (SSRIs) which reduce hyperactivity of the amygdala in response to fearful emotional stimuli, psilocybin is suggested to increase activation of the amygdala in response to positive emotional stimuli and has been shown to reduce anhedonia in one study. Psilocybin treatment may even affect brain plasticity, as demonstrated by the persistence of positive effects and increased amygdala response to positive emotional stimuli for up to a month post-treatment (Lowe et al., 2021).

A study used functional magnetic resonance imaging (fMRI) to investigate how psilocybin affects cerebral blood flow (CBF) and resting-state functional connectivity (RSFC). The study found that psilocybin treatment resulted in reduced symptoms of depression and decreased amygdala CBF, as well as increased RSFC within the default-mode network (DMN), specifically in the ventromedial prefrontal cortex-bilateral interior lateral parietal cortex, and decreased RSFC in the parahippocampal-prefrontal cortex. These changes in RSFC and the DMN are characteristic of mood and anxiety disorders and may be another mechanism by which psilocybin produces anti-depressant effects. The study also suggests that psilocybin may disrupt functional connectivity between the medial temporal lobe and the DMN (Szigeti et al., 2021).

In a different fMRI study, it was found that psilocybin treatment led to a decrease in functional connectivity between the amygdala and the ventromedial prefrontal cortex (vmPFC) in response to fearful and neutral faces. The vmPFC is responsible for a variety of functions such as emotional processing, cognitive behavior, and goal orientation, and it exerts top-down inhibitory control on the amygdala. The study suggests that psilocybin's ability to decrease functional connectivity between the amygdala and vmPFC in response to fearful and neutral faces also results in a decrease in the top-down inhibitory control that the vmPFC has on the amygdala, ultimately leading to increased amygdala activity. This effect is similar to the decreased functional connectivity between the amygdala and left rostral prefrontal cortex (left rPFC) observed in individuals with major depressive disorder who have not been medicated.

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Introduction to Microdosing

One practice that has gained popularity in recent years is microdosing, which involves taking small, sub-perceptual doses of a compound on a regular basis. The idea of microdosing is not a new concept; Indeed, it has been a part of medical research for years. As early as the 1960s, progenitors of the microdosing movement have been engaging in the practice. Only recently, however, has the concept been applied as a career performance enhancer (Editorial, 2023).

When it comes to microdosing with psychedelic drugs, there is no clear definition of a dose. According to one source, 1/5 to 1/20 of a recreational dose would be considered a microdose. In reference to mushrooms, 2 to 3 grams of dried mushrooms is the medium-strength dose, and 0.3 grams is the microdose (Grinspoon, 2022). According to Dr. Byran Kuhn, PharmD, a pharmacist and poison education specialist at Banner-University Medical Center Phoenix, microdosing is generally 10% of the usual therapeutic dose (Olsson, n.d.).

However, since mushrooms can vary greatly in their psilocin content, it is difficult to take these dosages as fact. Consistent research cannot be obtained due to the varying potency of the mushrooms (Kuypers et al., 2019).

The intended result of microdosing is to generate therapeutic results without the accompanying "high." These desired effects can include alleviating symptoms of mood disorders such as depression and anxiety as well as improving clarity and professional performance (Olsson, n.d.). LSD (Lysergic acid diethylamide) microdoses in relation to full LSD dosage show a similar trend to that of psilocybin microdoses. The average dose of LSD causes visual and auditory hallucinations, altered perceptions of time, paranoia, and expanded consciousness. However, a microdose of LSD which is 10-20 micrograms once every four days does not induce long hallucinatory experiences and it has many positive effects including increased emotional and physical energy, a sense of overall well-being, and creativity (Editorial, 2023).

Microdosing has been described as a way to enhance creativity, focus, and overall well-being without the intense psychedelic effects associated with higher doses of psilocybin. While there is still much to be learned about the effects of microdosing on psilocybin, early research suggests that it may have a positive impact on mental health and creativity.

Potential Benefits

A large study has demonstrated that individuals who microdose psilocybin exhibited enhanced mood and reduced anxiety, depression, and stress over a one-month period compared to those who did not take the compound (Shukla, 2022). This study is in line with evidence from mainly small observational studies that suggest microdosing psilocybin can increase physical energy levels, enhance cognitive tasks, alleviate symptoms of depression and anxiety, treat addiction, and promote emotional balance. The effects are subtle yet noticeable (Kuypers et al., 2019). It is worth noting that these positive changes in mood and mental health related to microdosing psilocybin were observed even in individuals with mental health issues. (Shukla, 2022).

Additionally, decreased reliance on traditional analgesic medications, such as aspirin and acetaminophen has been achieved by patients through self-administration of psilocybin, even at doses that do not induce a psychedelic experience and have minimal adverse cognitive or somatic effects, despite varying preparations and potencies. The efficacy of pain relief was further enhanced when combined with functional exercise, and in one case, repeated dosing appeared to provide increased relief, indicating a potential long-term plasticity-mediated effect. These findings underscore psilocybin's therapeutic potential in treating chronic pain, which necessitates further research (Lyes et al., 2022).

Studies on the Effects

A pilot study was conducted on psilocybin's effects on advanced cancer patients suffering from generalized anxiety disorder (GAD), cancer-related anxiety disorder, acute stress disorder, and existential distress. Patients in the study were given niacin (vitamin B3, active placebo) or a moderate dose of psilocybin at random. The group that received the psilocybin reported a reduction in symptoms of anxiety and depression, however, compared to the placebo group, it was not statistically significant. After six months, both groups showed a significant decrease in symptoms of anxiety and depression compared to baseline. In addition, individuals stated that they experienced better social interactions, gained new perspectives on how their illness impacted their lives, and developed a more optimistic outlook on their limited life expectancy as a result of psilocybin treatment. However, the treatment did not alleviate pain or decrease the need for pain medication. There were no serious adverse effects reported by the participants (Schimmers et al., 2021).

A randomized crossover study, conducted by Griffiths et al. (2016) and Ross et al. (2016), investigated the effects of a moderate to high dose (2-3 mg/70 kg and 0.3 mg/kg, respectively) of psilocybin compared to an active placebo in combination with preparatory and integrative psychotherapeutic sessions. The participants had life-threatening

cancer and related depressive disorders, with or without GAD, adjustment disorder, and anxiety and depression, or GAD with or without dysthymia. The crossover occurred 5 or 7 weeks after the initial dosing session. Griffiths et al. reported a significantly larger response and remission rate on depression and anxiety in the high-dose group compared to the active placebo group after 5 weeks, with 78% and 83% of all participants showing clinical responses on depression and anxiety compared to baseline at six months after crossover. Positive effects were also reported by participants, their friends, and family, including improvements in spiritual well-being, social contacts, quality of life, acceptance of death, and optimism, though psilocybin treatment did not reduce pain or the need for analgesic medication (Schimmers et al., 2021).

Another randomized crossover study included 29 participants and found significant response differences between the high-dose and low-dose groups. Before crossover, anxiety response was 58% versus 14%, and depression response was 83% versus 14%. After six months, there were significant decreases in anxiety (60%) and depression (80%). The treatment also reduced demoralization and hopelessness and improved spiritual well-being and quality of life, both short-term (after 2 weeks) and long-term (after 6 months). Death anxiety did not significantly decrease in the short term, but the high-dose group showed a significant improvement in attitude towards death after 26 weeks. Two additional follow-ups were conducted after 3 and 4 years in 14 participants, and reductions in anxiety, depression, hopelessness, and demoralization were still observed after 3 years. Death anxiety was significantly lower, and spiritual well-being was improved compared to baseline. After 4 years, 60-80% of patients still showed significant reductions in depression and anxiety compared to baseline. A significant correlation was observed between mystical experiences and therapeutic outcomes in both studies. Qualitative studies revealed that patients experienced other important outcomes, such as better insights into existing relationships, improved access to their feelings, increased self-acceptance and self-esteem, and acceptance of their illness (Agin-Liebes et al., 2020).

In 2020, an open-label pre-post study was conducted to investigate the effects of one psilocybin session combined with individual and group therapy on demoralized older long-term AIDS survivors with and without complex medical and psychiatric histories. The results showed significant reductions in self-reported demoralization, grief, and psychological trauma from baseline to end-of-treatment and after 3 months. (Anderson et al., 2020)

An intriguing result was found when administering psilocybin doses of 11 mg/70 kg and 15 mg/70 kg. They observed a noticeable reduction in global cerebral blood flow across various brain regions, including the frontal, parietal, temporal, limbic, cingulate, and occipital cortex, insula, caudate, putamen, pallidum, amygdala, hippocampus, and thalamus. The reduction in global cerebral blood flow observed after administering psilocybin may be associated with the psychological effects typically experienced with lower doses of the substance. (Lewis et al., 2017). This link can be explained by the complex interaction between psilocybin and the brain's neural networks.

Psilocybin affects the serotonin system in the brain, particularly the 5-HT2A receptors. These receptors are thought to be involved in the mechanism of action of antidepressant drugs such as SSRIs. Activation of these receptors leads to changes in neural activity and communication. The reduction in cerebral blood flow observed may reflect a decrease in overall brain activity or redistribution of blood flow to specific brain regions (Kuypers et al., 2019).

The psychological effects of psilocybin are thought to arise from the modulation of various brain networks involved in cognition, emotion, and perception. The decreased blood flow may reflect a temporary disruption in the normal functioning of these networks, leading to alterations in sensory perception, emotional processing, and thought patterns. Additionally, the regions showing reduced blood flow, such as the frontal, parietal, temporal, limbic, and cingulate cortex, are known to be involved in higher cognitive functions, emotional regulation, and self-awareness. Changes in blood flow in these areas may contribute to the profound alterations in perception, mood, and self-reflective processes often reported during psilocybin experiences. Additionally, the restoration of balance between the 5-HT1A and 5-HT2A receptors that is caused by using psilocybin is said to alleviate symptoms in individuals with OCD (Kuypers et al., 2019).

It is important to note that the exact mechanisms underlying the relationship between reduced blood flow and psychological effects are still being studied. Further research is needed to fully understand the complex neurobiological processes involved in psilocybin's effects on cerebral blood flow and its impact on subjective experiences.

Another concept that needs to be explored is the "expectancy effect". Many individuals reported that psychedelics have enhanced their concentration, mood, productivity, creativity, and ability to empathize with others. Individuals taking psychedelics are expecting the psychedelics to make them feel smarter and happier, so the dose does make them feel smarter and happier- regardless of what is in the pill, just from taking it (Bergström, 2017).

Risks and Concerns

While the potential benefits of microdosing with psilocybin are promising, there are risks and concerns associated with this practice. One concern is that the long-term effects of microdosing on psilocybin are still unknown. While studies have found no significant adverse effects of microdosing, it is essential to note that these studies have been conducted over a short period of time and on a relatively small scale. Microdosing is a relatively new and popular trend that is not well understood. While the risks of taking larger, recreational doses of popular drugs are known, there is little information about the potential dangers of taking small doses over a prolonged period. Medical researchers can only speculate about the potential risks of microdosing, such as tolerance, abuse, dependence, and addiction. Consistent exposure to potent drugs through microdosing could increase the risk of developing an addiction (Editorial, 2023). Since psilocybin is categorized as a Schedule I drug under the UN conventions, it is considered the most harmful and has no recognized value, which contributes to its lack of research. This classification imposes severe restrictions and penalties for unapproved possession, even for sub-psychoactive or microdose levels. In order to conduct research, ethical regulatory and institutional approvals are required. Dosing must occur in a secure environment such as a research ward or hospital, which adds a significant cost and complexity to any study of repeated microdosing (Kuypers et al., 2019).

The legality of psilocybin, which varies widely around the world, is another reason for concern. In many countries, individuals who choose to microdose may be breaking the law. Due to the potential legal consequences of possessing, buying, and using these substances, the sources are unregulated so the potency cannot be certain (Gupta, 2022). Psilocybin is found in around 200 species of fungi (mushrooms), and it is important to obtain mushrooms from a reliable source. Mistakenly ingesting poisonous mushrooms can cause liver damage, severe illness, or even death. It should be noted that taking any illicit substance can be harmful, even if the drug itself is not considered addictive. Illicit substances may be laced with other potent drugs, such as fentanyl, ketamine, or methamphetamines, which can be dangerous to consume (Grinspoon, 2022).

It is important to note that psilocybin is a potent psychedelic compound, and even small doses can have significant effects on mood and cognition. While microdosing is intended to minimize the psychedelic effects of psilocybin, there is still a risk of unintended and potentially negative effects. Psilocybin is generally considered safe at low dosages and has been used for centuries by indigenous populations. However, taking too high a dose can result in a terrifying or traumatic experience.

Critics express concern that unrestricted use of these drugs may harm individuals with mental health issues and may even trigger mental illnesses such as psychosis in vulnerable individuals. It is important to note that the use of all psychedelic substances should be approached with great care, if at all, in patients with serious mental illnesses such as bipolar disorder or schizophrenia. For safety reasons, these individuals are generally excluded from studies involving psychedelics (Grinspoon, 2022).

In 2019, a small research survey was conducted on individuals who were microdosing. Participants in the survey reported the following side effects: increased anxiety, migraines, headaches, problems thinking clearly, upset stomach, low energy, difficulty staying focused, appetite changes, low mood, difficulty with social interaction, and uncomfortable physical sensations such as tingling or numbness (Gupta, 2022). Another study was conducted in 2020, and although there were many positive results, two unanticipated incidents were recorded in the study. In one case, a patient intensely relived a traumatic occurrence (not associated with psilocybin) two days following the treatment, while in another instance, a participant experienced severe anxiety after feeling excluded by the group one week later (Schimmers et al., 2021).

Psilocin's activation of serotonin 5-HT2B receptors, along with other serotonin receptors, may cause cardiac valvopathies with repeated use. This is a serious potential adverse event, and some drugs have been withdrawn from the market due to similar concerns. Additionally, the use of high-dose psilocybin intake has been discredited, but there is still a risk of 5-HT2B receptor stimulation with repeated microdosing leading to tissue overgrowth. Although the efficacy of psilocin is lower than that of 5-HT, it still has a higher affinity for the 5-HT2B receptor, so further research is needed to fully understand the risks associated with microdosing (Kuypers et al., 2019).

Additional studies analyzed the effects of psilocybin and on animals. When animals were given a high dose of psilocybin (10 mg/kg), they experienced changes in their sympathetic nervous system, including irregularities in heart rate, breathing rate, dilated pupils, raised hairs, high blood sugar, and muscle tension. A study on rhesus monkeys found that injecting 2-4 mg/kg of psilocybin intraperitoneally also resulted in similar excitatory effects in the central nervous system (Kuypers et al., 2019). Compared to psilocybin, after examining rodents that were given repeated doses of LSD similar to microdosing, it was found that low doses of LSD given every other day for several

months resulted in long-lasting negative behavioral changes. These changes, which persisted for several weeks to months even after the LSD administration was discontinued, included increased aggression, scruffy appearance, anhedonia, and hyper-reactivity. The study also found that LSD produced alterations in gene expression in key cortical regions like the medial prefrontal cortex, which were enriched for schizophrenia and bipolar depression. These changes in gene expression lasted for a long time even after the drug was discontinued (Kuypers et al., 2019).

Results

A recent observational study involving 953 psilocybin microdosers over a 30-day period showed small to medium-sized improvements in mood and mental health, consistent across gender, age, and the presence of mental health concerns (Grinspoon, 2022). This and other similar studies seem to confirm anecdotal reports of benefits from microdosing.

The concept of the "expectancy effect" seems to play a large role. In a randomized controlled study, 34 patients were randomly assigned to receive either psilocybin or a placebo. Although subjective effects were reported, and some changes in brain waves were observed on an EEG machine, the researchers concluded that low-dose psilocybin did not result in objective improvements in creativity, well-being, and cognitive function. This study supports the theory that the perceived benefits of psychedelics at sub-perceptual doses are mostly due to expectancy effects, and higher doses are needed for therapeutic benefits (Grinspoon, 2022) Another study was conducted with 191 participants that supported the "expectancy effect" theory as well. The microdose group showed significant improvements in psychological measures, including well-being and life satisfaction, after the four-week period. However, the placebo group also improved, and there were no significant differences between the two groups. The results suggest that the anecdotal benefits of microdosing can be attributed to the placebo effect and that taking empty capsules, even with the knowledge that they might contain microdoses, can produce the same benefits. Although there were some small differences in acute and post-acute scales between the microdose and placebo groups, these could be explained by participants breaking blind. Overall, the study supports the hypothesis that the benefits of microdosing are due to psychological expectations rather than the microdose itself (Szigeti et al., 2021). To ascertain the validity of the claims made by microdosers, it is essential to conduct rigorous placebo-controlled clinical studies using various low doses of the drug. These studies would provide valuable scientific evidence regarding the actual effects of microdosing and help differentiate them from placebo effects or other confounding factors. By comparing the outcomes of individuals receiving microdoses to those receiving a placebo, researchers can objectively evaluate the specific benefits or potential drawbacks associated with microdosing. These studies would contribute to a more comprehensive understanding of the therapeutic potential, safety, and limitations of microdosing, informing healthcare professionals, policymakers, and individuals interested in exploring this approach (Kuypers et al., 2019).

Implications for Further Research

Further research on the long-term effects of microdosing with psilocybin is crucial to fully understanding the implications and potential risks of this practice. While there is a growing interest and anecdotal reports suggesting positive outcomes, rigorous scientific investigations examining the sustained effects and safety profile of microdosing are limited. It is important to evaluate potential changes in psychological well-being, cognitive functioning, and overall mental health over an extended period. Longitudinal studies that follow individuals who engage in microdosing for an extended duration are necessary to assess any potential adverse effects, including the possibility of developing tolerance, dependency, or other unforeseen consequences (Kuypers et al., 2019). Additionally, investigations into potential physiological changes and the impact on brain function are warranted to provide a comprehensive understanding of the implications of long-term microdosing. This research will provide valuable insights for individuals considering microdosing as a therapeutic or self-enhancement approach and inform healthcare professionals in providing evidence-based guidance and support.

Conclusion

Microdosing with psilocybin is a practice that has recently gained popularity as a way to enhance creativity, focus, and overall well-being without the intense psychedelic effects associated with higher doses of psilocybin. While the science behind microdosing is still in its early stages, the available research suggests that it may have potential benefits for mental health, creativity, and overall well-being. However, there are also risks and concerns associated with this practice, including the unknown long-term effects of microdosing and the legal status of psilocybin in many countries.

Overall, the available literature on microdosing with psilocybin is still limited, and more research is needed to fully understand its potential benefits and risks. Nonetheless,

the evidence that we do have shows the positive effects microdosing has on cognitive processes and emotional well-being. The growing interest in psilocybin as a potential therapeutic agent highlights the need for continued research in this area.

References

Agin-Liebes GI, Malone T, Yalch MM et al (2020) Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. J Psychopharmacology 34(2):155–166

Alshaikhli, H., Al-Naggar, R. A., & Erlam, G. (2021). Effectiveness of Psilocybin on Depression: A Qualitative Study. Electronic Journal of General Medicine, 18(3), em296. https://doi.org/10.29333/ejgm/10862

Anderson, B. D. O., Danforth, A. L., Daroff, R. B., Stauffer, C. S., Ekman, E., Agin-Liebes, G., Trope, A., Boden, M. T., Dilley, J. W., Mitchell, J. P., & Woolley, J. D. (2020). Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. EClinicalMedicine, 27, 100538. https://doi.org/10.1016/j.eclinm.2020.100538

Anderson, T., Petranker, R., Christopher, A., Rosenbaum, D. M., Weissman, C. R., Dinh-Williams, L., Hui, K., & Hapke, E. (2019). Psychedelic microdosing benefits and challenges: an empirical codebook. Harm Reduction Journal, 16(1). https://doi.org/10.1186/s12954-019-0308-4

Bergström, M. (2017). The Use of Microdosing in the Development of Small Organic and Protein Therapeutics. The Journal of Nuclear Medicine, 58(8), 1188–1195. https://doi.org/10.2967/jnumed.116.188037

Editorial. (2023, April 13). What Is Microdosing? | Is Microdosing Safe? | Oxford Treatment. Oxford Treatment Center. https://oxfordtreatment.com/substance-abuse/microdosing/

Fnp, K. D. (2023, March 14). What are magic mushrooms and psilocybin? https://www.medicalnewstoday.com/articles/308850#risks

Grandjean, J., Buehlmann, D., Buerge, M., Sigrist, H., Seifritz, E., Vollenweider, F. X., Pryce, C. R., & Rudin, M. (2021). Psilocybin exerts distinct effects on resting state networks associated with serotonin and dopamine in mice. NeuroImage, 225, 117456. https://doi.org/10.1016/j.neuroimage.2020.117456

Griffiths, R. R., Johnson, M. W., Carducci, M. A., Umbricht, A., Richards, W. A., Richards, B. D., Cosimano, M. P., & Klinedinst, M. A. (2016). Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. Journal of Psychopharmacology, 30(12), 1181–1197.

Grinspoon, P., MD. (2022). The popularity of microdosing of psychedelics: What does the science say? Harvard Health. https://www.health.harvard.edu/blog/the-popularity-of-microdosing-of-psychedelics-what-does-the-science-say-202209192819

Gupta, S. (2022, May 24). Everything You Need to Know About Microdosing. GoodRx Health. https://www.goodrx.com/well-being/substance-use/microdosing

Hesselgrave, N., Troppoli, T. A., Wulff, A. B., Cole, A. L. J., & Thompson, S. M. (2021). Harnessing psilocybin: antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT2R activation in mice. Proceedings of the National Academy of Sciences of the United States of America, 118(17). https://doi.org/10.1073/pnas.2022489118

Kuypers, K. P. C., Ng, L., Erritzoe, D., Knudsen, G. M., Nichols, C. D., Nichols, D. E., Pani, L., Soula, A., & Nutt, D. J. (2019). Microdosing psychedelics: More questions than answers? An overview and suggestions for future research. Journal of Psychopharmacology, 33(9), 1039–1057. https://doi.org/10.1177/0269881119857204

Lewis, C. R., Preller, K. H., Kraehenmann, R., Michels, L., Stämpfli, P., & Vollenweider, F. X. (2017). Two dose investigation of the 5-HT-agonist psilocybin on relative and global cerebral blood flow. NeuroImage, 159, 70–78. https://doi.org/10.1016/j.neuroimage.2017.07.020

López-Giménez, J. F., & González-Maeso, J. (2017). Hallucinogens and Serotonin 5-HT2A Receptor-Mediated Signaling Pathways. In Current topics in behavioral neurosciences (pp. 45–73). Springer Science+Business Media. https://doi.org/10.1007/7854_2017_478

Lowe, H. J., Toyang, N. J., Steele, B., Valentine, H., Grant, J., Ali, A., Ngwa, W., & Gordon, L. (2021). The Therapeutic Potential of Psilocybin. Molecules, 26(10), 2948. https://doi.org/10.3390/molecules26102948

Lyes, M., Yang, K., Castellanos, J. P., & Furnish, T. (2022). Microdosing psilocybin for chronic pain: a case series. Pain, 164(4), 698–702. https://doi.org/10.1097/j.pain.0000000000002778

Nichols, D. E. (2016). Psychedelics. Pharmacological Reviews, 68(2), 264–355. https://doi.org/10.1124/pr.115.011478

Nichols, D. E., Johnson, M. P., & Nichols, C. D. (2017). Psychedelics as Medicines: An Emerging New Paradigm. Clinical Pharmacology & Therapeutics, 101(2), 209–219. https://doi.org/10.1002/cpt.557

Olsson, R. (n.d.). What is Microdosing and Is It Safe? What to Know| Banner. https://www.bannerhealth.com/healthcareblog/teach-me/can-microdosing-psychedelics-boost-your-mental-health

Ross, S. L., Bossis, A. P., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B. H., Mennenga, S. E., Belser, A. B., Kalliontzi, K., Babb, J. S., Su, Z., Corby, P., & Schmidt, B. P. (2016). Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. Journal of Psychopharmacology, 30(12), 1165–1180. https://doi.org/10.1177/0269881116675512

Schimmers, N., Breeksema, J. J., Smith-Apeldoorn, S. Y., Veraart, J. K. E., Van Den Brink, W., & Schoevers, R. A. (2021). Psychedelics for the treatment of depression, anxiety, and existential distress in patients with a terminal illness: a systematic review. Psychopharmacology, 239(1), 15–33. https://doi.org/10.1007/s00213-021-06027-y

Shukla, D. (2022, July 25). Microdoses of psychedelic mushrooms may improve mood and mental health. Medical News Today. https://www.medicalnewstoday.com/articles/microdoses-of-psychedelic-mushrooms-may-improve-mood-and-mental-health

Szigeti, B., Kartner, L., Blemings, A., Rosas, F., Feilding, A., Nutt, D. J., Carhart-Harris, R. L., & Erritzoe, D. (2021). Self-blinding citizen science to explore psychedelic microdosing. eLife, 10. https://doi.org/10.7554/elife.62878