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‘Shrooms for the Blues: Psilocybin to alleviate difficult-to-treat depression

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Abstract

Depression is a devastating disease, affecting hundreds of millions of people worldwide. Cases of difficult-to-treat depression are also increasingly common, exposing the ineffectiveness of currently available treatments. This paper reviews evidence supporting the use of psilocybin, the prodrug found in psychedelic mushrooms, as a potential antidepressant for treatment-resistant and cancer-related depression, two prevalent kinds of difficult-to-treat depression. Through its interactions with the serotonin system, psilocybin appears to create positive and enduring effects on mood that are fundamentally different from conventional antidepressants. Despite concerns about psilocybin’s potential to cause neurotoxicity or psychosis, trials have shown this drug to be quite safe, especially when administered in small doses in a clinical setting. These studies suggest that, both neurologically and psychologically, psilocybin has led to previously unreachable successes for patients struggling with cancer-related and treatment-resistant depression.

Keywords

Neuroscience, Psilocybin, Depression, Psychedelics, Hallucinogens, Antidepressants, Treatment-resistant depression, Cancer-related depression

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Introduction

Taking a hallucinogenic trip may not be the first thing that comes to mind when thinking about how to treat mood disorders. However, psilocybin, the psychoactive prodrug compound found in hallucinogenic ("magic") mushrooms, may hold the key to treating specific cases of depression.

People worldwide struggle with clinical depression, also known as major depressive disorder (denoted simply as "depression" in this manuscript). Associated with decreased levels of the neurotransmitter serotonin in the brain, depression manifests itself with symptoms such as sadness, hopelessness, loss of energy and motivation, and suicidality.

Depression is a highly prevalent mental illness that affects millions of people with devastating worldwide impact. In the US, at least 1 in 5 adults experiences depression sometime in their life (1), and it costs the nation $200 billion annually in the form of direct medical costs, decreased productivity, and the societal costs of suicide (2). In research conducted by the World Health Organization (3), depression was ranked as the single largest contributor to global disability. It is also the largest risk factor for suicidal behavior, which kills around 800,000 people per year. In 2015, the WHO estimated that roughly 4.4% of the world population—over 300 million people—had depression.

Depression's prevalence had been steadily increasing in the US even before the COVID-19 pandemic; between 2005 and 2015, the prevalence of past-year depression across all demographics increased by over 0.5% (1). The stressors of the pandemic may have increased that rate three-fold (4).

Circumstantial or environmental factors, such as physical illness or financial stress, are not the only risk factors for depression; genetics can also play a role. For example, inheriting different polymorphs of the gene encoding the serotonin transporter protein, responsible for transporting serotonin out of the space between neurons, can make someone more susceptible to depression (5).

Drugs used to treat depression are some of the most prescribed medications on the market (5). Selective Serotonin Reuptake Inhibitors (SSRIs) are the most widely prescribed class of antidepressants because they are seen as generally safe and effective. However, SSRIs are not without flaws. They are slow to act, and the brain can quickly build up a tolerance to them. After long treatment courses, many people–more than a third–experience treatment-resistant depression, in which their symptoms do not adequately respond to conventional antidepressant treatment (6). In such cases of treatment-resistant depression, new alternatives to conventional treatments must be utilized to alleviate symptoms.

There are other instances where SSRIs are insufficient or ineffective, such as in cancer-related depression. SSRIs do not alleviate symptoms fast or consistently enough to support depressed patients with a life-threatening oncologic diagnosis. Side effects can also jeopardize patients' treatment adherence. Additionally, it seems as though the existential distress experienced by cancer patients with a life-threatening diagnosis is a crucial part of their depression, and this aspect is not at all addressed by conventional antidepressants.

Treatment failures like those listed above have inspired the search for alternative ways to treat these cases of depression. Surprisingly, psychedelic drugs may offer a viable alternative, and psilocybin appears to be one of the most promising in this regard.

There are many misconceptions when it comes to psychedelic drugs. Many falsely associate psychedelics with neurotoxicity or abuse, even though these drugs have a very low potential to cause either. While there are some known severe adverse effects, many are overstated in their prevalence or severity, and can be avoided when low doses are administered in a clinical setting (7, 8).

Like SSRIs, psilocybin interacts with the serotonin system in the brain. However, the specific neurons and receptors it exploits are different, and the user has a very different subjective experience. The emotional, spiritual, and existential aspects of the psilocybin "trip" may be an integral part of its efficacy, particularly in treating cancer-related depression. What's more, psilocybin's anxiolytic and antidepressant effects may last for months after a single low dose, a duration of efficacy far beyond that of any other antidepressant treatment (9).

This manuscript will describe the basis of depression and the proposed mechanisms of psilocybin's functionality. Psilocybin's possible use as an antidepressant will be discussed, especially in certain abnormal cases of depression, by reviewing key studies and meta-analyses. There are many types of atypical depression, but this manuscript will focus on two: cancer-related and treatment-resistant depression. These are two types of depression where conventional treatments have markedly failed to support patients, and where the most robust research has shown psilocybin's potential as an antidepressant. Although more research is needed to fully understand its long lasting efficacy, psilocybin may offer a safe and highly effective alternative to struggling patients with cancer-related and treatment-resistant depression.

Depression

The neurochemistry of depression is not well understood, but it is widely agreed that depression is generally associated with decreased levels of serotonin in the brain (5, 9-12). Serotonin (5-hydroxytryptamine or 5-HT) is a neurotransmitter, or a chemical messenger, in the brain. It helps regulate mood and emotions, and modulates sleep, appetite, digestion, blood clotting, and sexual function.

Serotonin is synthesized and released by 5-HT neurons. There are relatively few 5-HT neurons in the brain (just 250,000 out of 10^{11} total neurons) but their axons reach all brain areas (13), making this type of neuron essential to almost all brain functions, and implicated in many brain pathologies. 5-HT receptors (responsible for detecting serotonin) and presynaptic 5-HT reuptake sites (responsible for removing serotonin from the intracellular space) are distributed differently in the brain regions of depressed people and suicide victims (11). Therefore, serotonin is released and reabsorbed in differing levels across brain regions, creating a hierarchical gradient across the brains of depressed people (14).

The activity of the 5-HT system is controlled in multiple ways, including by inputs from brain

areas such as the forebrain or pons, but an especially important mechanism is that of self-inhibition. Activation of self-inhibitory autoreceptors in the presynaptic neuron pauses the neuron's firing, creating a tightly controlled negative feedback loop. In a depressed brain, lower amounts of serotonin are released from the presynaptic 5-HT neuron. To try to overcome this disparity, the self-inhibitory feedback mechanism is exploited by SSRIs. These drugs can increase the concentration of serotonin in extracellular brain spaces by interacting with the presynaptic neuron to prevent serotonin reuptake (13, 15). This process will be discussed in more detail below.

Above the cellular level, depression compromises functionality on a brain-wide scale. The hippocampus, prefrontal cortex, and amygdala regions of the brain are thought to play major roles in mood and emotion (13). The hippocampus is involved in cognitive functions such as memory and attention and is included in limbic circuits thought to be involved in the expression and apprehension of emotion. The hippocampus is often affected by mood disorders. Postsynaptic 5-HT_{2A} receptors (a subtype of the 5-HT receptor) in the hippocampus of depressed people have reduced binding capacity, and suicide victims present with 5-HT_{2A} receptor hypersensitivity (11). People with depression also tend to have reduced hippocampal volumes (10).

The prefrontal cortex (PFC) and amygdala are frequently affected by depression. The PFC is involved in personality expression, decision making, and complex cognitive behavior (16). Reduced overall activity in the PFC (11) and structural irregularities are observed in people with depression (16). The pathophysiology of depression includes the atrophy of neurons in the PFC. In a depressed brain, this region's neurons can lose synapses, dendritic spikes, and neurites (17). Additionally, depression can impact the amygdala. The amygdala is critical in emotional processes and responses. This region is responsible for making decisions in the face of emotional stimuli and has direct connections with parts of the PFC and hippocampus. Different response mechanisms (17) and reduced volumes of the amygdala (10) are observed in people with depression.

Finally, depression and the functionality of certain high-order brain networks are related. The default mode network (DMN), executive network (EN), and salience network (SN) are networks of interconnected brain regions associated with certain high-level cognitive functions. The DMN is associated with self-referential thinking and introspection, while the EN is involved with cognitive control, and the SN is associated with attentional switching. These networks can all be implicated in depression and when their functionality is impaired, people can experience "cognitive rigidity" and suffer from cycles of repetitive negative thinking (Figure 1). Research suggests that depressive symptoms correlate with reduced signal and information processing and sharing between these networks (19).

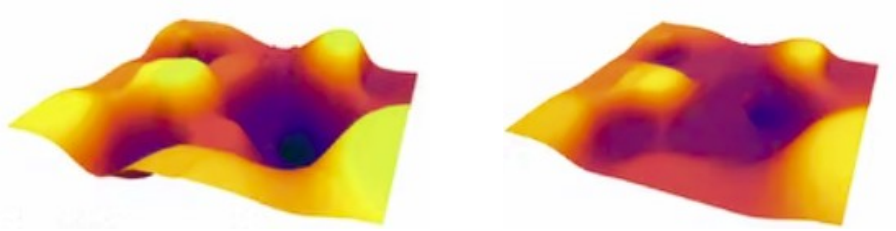

Figure 1: The depressed brain can be envisaged as a deeply undulating topology (left image) that makes communication between the DMN, EN and the SN brain networks difficult. Psylocybin 'flattens' this landscape (right image) and alleviates rigid 'deep well' thought patterns. Adapted from reference 19.

Experts still do not completely understand how to optimally treat this behavioral health disorder. Depression stems from many unique causes; shares symptoms with comorbid disorders, such as anxiety; and is not completely understood neurobiologically. These factors have impeded the development of effective treatments for depression (5).

Conventional antidepressants

Despite being some of the most prescribed drugs across the world (5), antidepressants have serious shortcomings. No single class of antidepressant is without serious flaws, and conventional antidepressants are widely ineffective when it comes to treating certain types of depression, namely cancer-related and treatment-resistant depression. Both of these will be discussed in further detail later in this manuscript.

SSRIs were developed in the 1980s (5), and three decades later remain by far the most popular antidepressants on the market. As mentioned above, SSRIs prevent the reuptake of serotonin (5-HT), specifically, by raphe nuclei neurons, which are the neurons responsible for releasing this neurotransmitter into the rest of the brain. After the serotonin carries a message across a synapse from one neuron to another, it is usually reabsorbed by the presynaptic neuron through the process of reuptake. SSRIs function by inhibiting serotonin reuptake, specifically by interacting with the presynaptic 5-HT_{1A} autoreceptors (13), keeping the neurotransmitter in the synapse and raising levels of serotonin in the intracellular space. This allows the serotonin to rebind to the postsynaptic neuron multiple times, restimulating it and increasing cellular responses.

However, SSRIs are far from perfect. They are slow to act and do not have optimal efficacy, especially in certain subtypes of depression. People's brains also become desensitized or build up tolerance to SSRIs, meaning they have less of an effect the longer someone takes them (13). Prolonged exposure to SSRIs desensitizes the self-inhibitory feedback loops in the 5-HT system that the drug interacts with, weakening the drug's ability to impact the system over time (15). SSRIs can also cause some adverse effects, such as hyponatremia, weight gain, and sexual dysfunction (20).

While the most common, SSRIs are not the only conventional antidepressants in use today.

Tricyclic antidepressants (TCAs) are considered to be the historical "gold standard" when it comes to antidepressant efficacy. Unfortunately, patients using TCAs can experience an array of adverse side effects, including urinary retention, blurred vision, and cognitive dysfunction. The most dangerous side effects caused by this class of antidepressant are cardiovascular; they can cause cardiac conduction delays and cardiotoxicity after accidental or intentional overdose. In fact, these antidepressants are rated as the class of medication responsible for the most deaths by poisoning in the US. Likely because of these side effects, TCAs are underdosed by physicians and have very high noncompliance rates (20).

Another class of antidepressants is the monoamine oxidase inhibitors (MAOIs). These antidepressants' efficacy is quite well established, and they are thought to offer advantages when it comes to certain subtypes of depression, such as "atypical depression." However, MAOIs' clinical use has been limited because of their tendency to cause hypertensive attacks when ingested with certain foods or medications. Patients taking MAOIs must limit their diets and avoid many popular food items. Additionally, these antidepressants can cause a variety of other side effects, such as dizziness and weight gain, and dosing regimens are complicated and inconvenient (21).

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are also generally effective and may even have a faster onset of therapeutic effects than other antidepressants. However, SNRIs interact with other medications metabolized by the same enzymes, such as the antipsychotic haloperidol, which can result in adverse effects (21). SNRIs can also affect the cardiovascular system, analogous to TCAs, although with slightly lower risk of adverse outcomes (20).

SSRIs remain the most familiar and widely prescribed antidepressants, and contemporary research on alternative antidepressant treatments often uses SSRIs as comparators. This manuscript will follow this norm and compare psilocybin to SSRIs to illustrate its relative efficacy.

Psychedelics

Psychedelics are a class of drug known for producing hallucinations and infamous psychoactive experiences. Studies are beginning to show that these drugs may have more to offer the world than recreational use. Specifically, psilocybin and lysergic acid diethylamide (LSD) have been subject to research as possible antidepressants or anxiolytics (anti-anxiety drugs).

Psilocybin is the prodrug found in psychedelic mushrooms (Figure 2). Psilocybin is metabolized into the active compound psilocin in the body, which mediates the psychoactive effects experienced by the user. It has been used in spiritual and holistic practices, particularly in indigenous societies, for thousands of years.

Psilocybin, along with other plant-based psychedelics, has been used for healing for millennia, but psychedelics remained on the outskirts of American scientific culture until the mid-20th century. When the first English-language report on LSD was published in 1950, it enjoyed a period of great relevance in the psychological and psychiatric spheres. In the early 1950s, psychedelics, especially LSD,

became routinely used in research and even in clinical psychotherapy (20). Initial research conducted on LSD in the 1960s found largely positive results of its clinical potential without adverse side effects (8). Psychedelics were even researched as a specific treatment for psycho-spiritual distress in cancer patients during the 1960s (9).

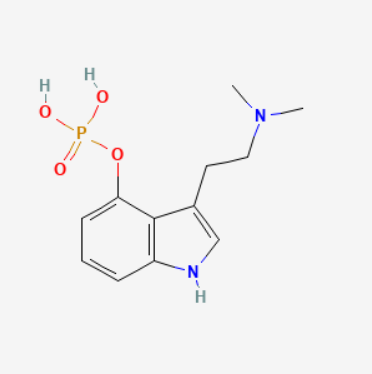

Figure 2: Chemical structure of Psilocybin, sourced from https://pubchem.ncbi.nlm.nih.gov/compound/Psilocybine#section=2D-Structure

This experimentation came to a halt as psychedelics came to be associated with the counterculture movements of the time (8). In 1970, psychedelics were included in the list of drugs illegal to manufacture, possess, and distribute under the Controlled Substances Act (9). LSD was banned under the 1971 UN Convention, and many countries soon criminalized other serotonergic psychedelics (8).

After a 25-year interlude, psychedelics have reentered the scientific sphere (23), perhaps because the need for alternative treatments for mood disorders has been more fully realized. This revival began in the 1990s and has been steadily growing since. Despite being studied much less than LSD in the 1960s, psilocybin specifically has entered the contemporary clinical sphere at an unprecedented scale (8). The clinical world of the 1960s was aware of psilocybin, but research favored LSD. However, much more robust contemporary research on psilocybin has discovered its surprisingly positive antidepressant potential. Other psychedelics have also come under study in the contemporary world of therapeutic research, such as ayahuasca and its anti-addiction properties and methylenedioxy methylamphetamine (MDMA) in treating Post Traumatic Stress Disorder (7).

It is not clear exactly how hallucinogenic compounds mediate their antidepressant (12) or psychoactive effects, but there is evidence that they all rely upon 5-HT_{2A} receptor activation (24). Cortical 5-HT_{2A} receptor expression is generally higher in depressed and suicidal people, but these receptors are not directly affected by SSRIs (12). Psilocin, however, is an agonist for 5-HT_{2A} receptors, implying that it can bind to these specific serotonin receptors to activate a neural response (2, 24). When psilocybin is metabolized into psilocin in the

body, it can interact with these receptors, inducing a deep shift in consciousness, resulting in dream-like imagery, enhanced introspection, and changes in emotional regulation.

One of the biggest challenges when it comes to using pharmaceuticals is the potential risks of unwanted side effects. The psychological and physiological long-term risks of psychedelics are not fully understood (8) and do warrant continued in-depth research before they can be fully approved for therapeutic use. However, there are many misconceptions when it comes to the dangers of psychedelics.

Some popularly held beliefs about psilocybin, and even psychedelics in general, are thoroughly misconceived. Despite frequent concerns about dependence, abuse, neurotoxicity, and overdoses, collectively, these pose a very small threat, if any at all. Psychedelics do not seem to lead to dependence or withdrawal symptoms, and these drugs are consistently rated low with respect to compulsive use and dependence risk (8). Additionally, psychedelics seem unlikely to cause addiction because they interact with the serotonergic system, while addiction is generally linked to the dopaminergic system (12). Psychedelics have a much lower potential for abuse compared to other psychoactive drugs.

In the 1960s, some studies were published suggesting that psychedelics were neurotoxic, and use could cause cognitive or neurological defects. These studies received a lot of attention, attention that was not sustained when most of them were refuted or retracted. Many researchers now agree that psychedelics are physiologically safe, even when used in high doses. In a similar vein, it is not easy to overdose on psychedelics. Overdose deaths can occur, but only when ingested in significantly high doses (23 times the standard dose for LSD) or when mixed unsafely with other drugs. In fact, psilocybin is rated among the lowest risk of death of all substance abuse categories (8).

However, psychedelics do have some concerning side-effects. With unprepared users or in unsafe settings, psychedelics have the potential to provoke dangerous behaviors, such as self-harm attempts or violence. However, instances of this are uncommon, especially when compared to other psychoactive drugs, and are often sensationalized in the media. Set (the expectation and experience of the user) and setting (the external environment) are crucial to avoiding harms. Under clinical conditions, the factors that can lead to dangerous behavior, such as lack of physical or social comfort and high dosage, can be mitigated (8).

Psychedelics have also been linked to the onset of schizophrenia and other psychoses. Fears of LSD-induced psychosis was a major factor in its criminalization. Early research on psychedelics ignored the importance of set and setting, raising the risk of adverse side effects. This risk is significantly decreased in contemporary clinical environments, especially thanks to the practice of psychiatric screening (8). When those with predispositions to psychotic illnesses are excluded, the probability of serious mental health effects is considerably reduced (25).

Hallucinogen Persisting Perception Disorder (HPPD) is a neurological visual processing disorder that results in visual experiences resembling those of psychedelics that are sustained while not under the influence of any drugs. Despite the common belief that psychedelics frequently cause this disorder, HPPD is not psychedelic specific; it can also be caused by other psychoactive substances like alcohol or benzodiazepines. Again, the exact cause of this disorder is not well understood, but sparse evidence suggests that it may be triggered as a sort of post-traumatic response after experiencing anxiety or panic during drug use (8). There are contradicting findings about the prevalence of HPPD in psychedelic users: some studies have found up to a 4.2% rate in users (26), but the modern era of psychedelic research, which has involved thousands of participants across decades, has not shown such high prevalence. It appears that clinical settings and screenings decrease the frequency of HPPD (8).

Perhaps the most well-known of the psychedelic adverse effects are the infamous challenging experiences (known colloquially as "bad trips"). These psychological experiences are characterized by distressing emotions, individuals putting themselves or others at risk, and enduring psychiatric effects. But surprisingly, bad trips are not always a uniformly bad thing: bad trips were considered among five worst lifetime experiences in a recent survey of hallucinogen users but were also associated with enduring increases in well-being (24). Research has also found that unpleasant experiences like these are transient and do not diminish the positive impact of the drugs on depressive symptoms (2). More research is needed to understand the neuropsychological basis of bad trips, but it appears like setting and dosage are again key influences, both of which can be controlled in a clinical setting (8).

Like all other pharmacological antidepressant treatments, the therapeutic use of psychedelics can occasionally cause serious side effects, but the public perception of these risks is greatly exaggerated. Many perceived dangers do not actually apply to psychedelic use, such as dependence or neurotoxicity. Others do have the potential to harm the user but drop greatly in prevalence when administered in a clinical setting. So far, psilocybin's potential benefits (discussed below) seem to outweigh its potential risks. In fact, experts consistently rate psilocybin as the potentially most beneficial and least harmful "drug of potential misuse" (7). In carefully selected patients, in a controlled setting, and with access to therapy and emotional support, these drugs are just as safe, if not safer, than other psychoactive drugs with better reputations (8).

Psilocybin as an antidepressant

Conventional antidepressant treatments have failed to help many with treatment-resistant or cancer-related depression, leading researchers to investigate psilocybin as another option. More research is needed, but studies suggest that psilocybin may be a viable alternative (7, 9, 12, 28).

In cancer-related depression

Patients with life-threatening cancer experience high levels of depression, and conventional treatments are especially ineffective in this demographic: reduction of symptoms is slow, relapse is high, and side effects can jeopardize treatment consistency (9). Chronic anxiety and

depression associated with life-threatening cancer diagnoses can result in decreased cancer treatment adherence and quality of life, and increased suicidality and prolonged hospitalization (12). Currently, there are no FDA-approved pharmacotherapies for psychological distress related to cancer (9).

Existential and spiritual wellbeing correlate with improved quality of life and decreased depression and suicidality in cancer patients. Increasingly, the need to mitigate existential distress in cancer patients has been recognized, and improvement in this area has been acknowledged as a vital aspect in treating cancer-related depression.

Ross et al. (9) studied the potential of psilocybin as an antidepressant and anxiolytic in cancer patients. The patients had all been diagnosed with clinically significant anxiety and depression in addition to life-threatening cancer. They were randomly assigned one of two oral dosing sequences: psilocybin (0.3 mg/kg) followed by niacin (the control; 250 mg) or vice versa. The primary outcome measures for this study were anxiety and depression and the secondary outcome measures included manifestations of cancer-related existential distress, such as hopelessness and demoralization, spirituality, and quality of life.

The psilocybin-first group maintained significant reductions in anxiety and depression at each time point throughout the study. The psilocybin-second group did not show any significant reductions in anxiety or depression until dosed with psilocybin. Immediately after their dose of psilocybin, they showed significant reductions which were maintained through the end of the study. At 6.5 months after the study, antidepressant and anxiolytic response rates were still elevated, to 60-80%.

In both the short term (2 weeks) and long term (6.5-month checkup), psilocybin produced reductions in hopelessness and demoralization and improvements in quality of life and spiritual wellbeing. In a 26-week post-dose 2 follow up assessment, it also produced improvements in attitudes towards death. After just the first dose, the psilocybin-first group showed higher positive effects on attitudes towards life and self, spirituality, and behavior. 87% of patients reported increased wellbeing or life satisfaction attributed to their psilocybin session. There were no serious adverse effects attributed to either the psilocybin or the niacin.

This study shows the novel finding of a single medication dose resulting in immediate and sustained clinical improvement for anxiety and depression in a population that has been extremely difficult to treat effectively. The study's results suggest that, in conjunction with psychotherapy, a single dose of psilocybin may produce lasting benefits for 7 weeks, and possibly even enduring up to 8 months post-dose. In previous studies, antidepressants have failed to produce significantly better results than placebos in the treatment of cancer-related depression, and this study suggests that psilocybin may offer a wholly new and much more effective regimen.

Psilocybin's ability to address cancer-related existential distress cannot be overlooked. This is a unique symptom that is not addressed by conventional antidepressants. The spiritual or existential aspects of psilocybin's effects that can deal with this distress could be an integral

part of its success. In cancer patients, the subjective mystical experience correlated with clinical benefits (reductions in depression and anxiety) for 6 weeks post-dose (9).

Vargas et al. (12) conducted a meta-analysis on 3 studies with 92 total patients with depression and anxiety associated with life-threatening disease (mostly cancer). The patients received between 0.2 and 0.4 mg/kg psilocybin, depending on the trial. While there were some transient cases of nausea, psychological distress, and/or physiological discomfort, no serious adverse effects were reported. The patients were all closely monitored in relaxed environments, potentially mitigating risks such as HPPD.

The meta-analysis found that psilocybin caused significant decreases in depressive and anxious symptoms. These reductions occurred independently of the dosage administered. Psilocybin doses also resulted in statistically significant antidepressant and anxiolytic effects lasting up to 189 days. While small, this meta-analysis shows that psilocybin's antidepressant potential to date has been statistically significant and illustrates another example of the medication's benefits enduring for months. However, it also brings to light the lack of data that currently exists on this topic.

Meta-analyses are conducted to statistically consolidate information gathered from many studies. The authors could only identify three high quality studies, highlighting the need for more research. As this is a controversial treatment with life-changing implications, any decisive statements or conclusions should await additional more robust research findings.

In treatment-resistant depression

New therapeutics are also needed for treatment-resistant depression. Treatment-resistant depression occurs when depressive symptoms do not respond significantly to conventional treatment strategies, usually including antidepressant drugs and counseling therapy. Of patients treated for depression, 70% of patients will not achieve full remission (20), and more than a third will become resistant to treatment (6). The next steps in treating treatment-resistant depression can include increasing doses, combining medications, or electroconvulsive therapy (ECT), but these treatments pose risks of increased toxicity or, in the case of ECT, memory loss (12).

Trials of psilocybin in treatment-resistant depression have shown promising results. Carhart-Harris, Bolstridge, et al. (7) conducted a trial on patients with moderate-to-severe unipolar depression that was unresponsive to two courses of pharmacologically distinct antidepressants taken for an adequate duration. They observed that after just 2 oral doses of psilocybin (10 mg and 25 mg, administered 7 days apart), all 19 participants of the study experienced reductions in depressive symptoms. Suicidality was significantly decreased at 1-, 2-, and 5-weeks post-treatment. None of the patients sought out antidepressants within 5 weeks of the psilocybin doses and symptom improvements remained significant for 6 months. There were no serious adverse effects. Patients reported feeling strong senses of unity and blissful states of being, and the researchers found a significant correlation between spiritual outcomes and alleviation of depression symptoms, as was noted in psilocybin studies in cancer-related depression.

Treatment-resistant depression can be caused by medication non-compliance (skipping doses, not staying on long enough, etc.). Psilocybin's exceptionally long duration of action allows it to potentially sidestep these issues. If one small dose can alleviate symptoms for weeks, if not months, patients will likely be able to better adhere to their treatment regimen because they will have to take many fewer overall doses. The brain cannot build tolerance against psilocybin's autonomic impacts (8), avoiding another cause of treatment-resistant depression.

Another study on psilocybin's alleviation of treatment-resistant depression was performed by Watts et al. (28). The purpose of this paper was, in addition to understanding psilocybin's objective antidepressant effects, to identify patients' subjective feelings towards the value of psilocybin as a treatment. The subjects of this study were the same subjects as those in Carhart-Harris et al. (7), described above. Where that study aimed to report on the clinical outcomes of psilocybin on treatment-resistant depression, this study sought to address the psychological mechanisms behind psilocybin's successes.

Six months after receiving their 25 mg psilocybin dose, patients were interviewed about their experience. They described depression as a disconnection—from the self, others, and the world—and reported personal histories of avoiding painful feelings. The patients reported that psilocybin helped them find feelings of reconnection and confront and accept their painful emotions. Additionally, they often described previous treatments as mirroring and perpetuating the disconnection created by depression, while the psilocybin treatment was able to work in the opposite direction. Therefore, they saw psilocybin as a welcome and intrinsically valuable alternative. Every patient in the study preferred psilocybin to any previous treatments they had tried.

The importance of the subjective and psychological aspects of these treatments cannot be overstated. Depression is a mood disorder, with the most palpable of its symptoms being psychological. Disenchantment with conventional treatment occurs when this emotional isolation–from one's surroundings and from oneself–caused by depression is reinforced (25). Future research should continue to report qualitative and subjective psychological findings to strengthen and flesh out conclusions.

Mechanisms of action

Psilocybin interacts with the serotonin system, specifically through the 5-HT_{2A} receptors, which seems to be involved in depression. 5-HT neurons, and therefore serotonin, are not evenly distributed throughout the brains of depressed people. Psilocybin therapy appears to lower this gradient between brain regions, making the distribution of serotonin across cortices more equal (14).

As mentioned earlier in this paper, three major brain areas affected by depression are the hippocampus, the prefrontal cortex, and the amygdala. It turns out that psilocybin also influences these same brain regions, perhaps pointing to another way this drug mediates its antidepressant effect.

The hippocampus is involved with memory and emotion. Reduced 5-HT_{2A} receptor binding capacity (11) and volumes of this region are

found in depressed patients (10). Neurogenesis (the birth of new neurons) can occur in the hippocampus throughout a person's life. Psychedelic drugs such as psilocybin, can stimulate hippocampal neurogenesis, which in turn modifies aspects of memory and learning. Psychedelic-mediated hippocampal neurogenesis appears to correlate with the alleviation of depression symptoms (29).

The atrophy of neurons in the prefrontal cortex may play a significant role in depression. Specifically, in a depressed brain, these neurons can lose their dendritic spines, and synapses may be eliminated. These structural changes can potentially be counteracted by a compound capable of promoting new growth and plasticity in the prefrontal cortex. Studies have shown that psilocybin is able to play this role; it appears to promote both the growth of new stable dendritic spines and synaptic strength in PFC neurons (17, 30).

Psilocybin may also bring about its antidepressant effects through deactivation of the medial prefrontal cortex (mPFC) (12). The mPFC is involved with decision-making, especially to emotional stimuli. The mPFC also has a close relationship with the hippocampus. The PFC is one of the most consistently implicated brain regions in depression (18), and the mPFC specifically tends to be hyperactive in depressed patients. Research shows that psilocybin's subjective psychoactive effects correlate with decreases in mPFC activity, returning the patient's mPFC activity closer to normal (12).

Psilocybin may also be able to reduce the amygdala's activation to threat-related stimuli. Carhart-Harris, Roseman, et al.'s (31) study on psilocybin revealed a relationship between the drug, depression, and the amygdala. fMRI brain scans revealed that cerebral blood flow significantly decreased post-psilocybin dose in parts of the amygdala. The researchers also found a significant relationship between reductions in cerebral blood flow in the amygdala and reductions in depressive symptoms. High amygdala activation to negative stimuli correlates with negative moods in depressed patients. In addition to perceiving risk, the amygdala is also very important in generating moods (12). Amygdala stabilization responses may be among the most important mechanisms of psilocybin's action.

In addition, psilocybin may be able to reduce depressive symptoms by increasing integration between high-order brain networks, namely the default mode network (DMN), executive network (EN), and salience network (SN) (Figure 1). These networks are comprised of cooperating brain regions and have to do with self-referential thought, cognitive control, and attention, respectively. When these networks are implicated in depression, people can experience cycles of negative thoughts. fMRI scans following two doses of psilocybin (10 mg/kg and 25 mg/kg one week apart) revealed that brain modularity was decreased, meaning that these global networks' functional connectivity was increased. The researchers found that decreased modularity just one day after psilocybin therapy correlated with long-term improvements in depression symptom severity, with clinical improvements lasting throughout the 6-month checkup. No changes in modularity were observed among the control group who were given the SSRI drug escitalopram, indicating that this antidepressant

action of increasing high-order brain network connectivity may be unique to psilocybin (19).

Acknowledging imperfect evidence

Despite psilocybin's potential, there is still very little high-quality evidence supporting or refuting its use. As of August 20, 2022, a search on Clinicaltrials.gov for "depression" + "psilocybin," filtered for completed studies only, resulted in only eight studies. Only four of those eight have reported their results. While the work so far has shown very promising data, we can only take these as early-stage preliminary findings to motivate future research, not to make any clinical recommendations.

Further, not all research so far has shown the same degree of promise. In a 2021 study published in the New England Journal of Medicine, Carhart-Harris et al. (32), researchers sought to compare psilocybin directly with escitalopram, an SSRI. Their primary outcome was improvement from baseline scores on the QIDS-SR16, a self-reported questionnaire used to measure depressive symptoms. The QIDS-SR16 is measured out of 27 points, with higher scores indicating more severe symptoms. At 6 weeks, they were unable to find an enduring significant difference in the primary outcome between the psilocybin group and the escitalopram group. However, the secondary outcomes of this study, including remission according to the QIDS-SR16 (defined as a score of 0-5), generally favored the psilocybin group. Additionally, this trial was conducted on patients with moderate-to-severe depression, but not specifically cancer-related or treatment-resistant depression. It is unclear whether these recent findings apply to these depression sub-types.

Carhart-Harris et al.'s (32) manuscript suggests another important question that remains unanswered or neglected: do current tests adequately measure depression? Depression is often measured using self-report tests such as the QIDS-SR16. These tests survey patients' mood symptoms like "feeling sad" or "feeling restless" and physical symptoms such as increases or decreases in weight and energy level. These tests may miss the more nuanced well-being symptoms such as those improved by psilocybin. For example, neither the QIDS-SR16 nor the GRID-HAMD-17 (another commonly used self-reported test) ask about ego and/or narcissism, psychological flexibility, violent behavior, or feelings of disconnectedness. These are all often negatively affected by depression and improved by therapeutic use of psilocybin (33). Both patients and researchers would benefit if self-reporting studies included questions on these more nuanced psychological symptoms. For example, Carhart-Harris et al.'s (32) manuscript could have resulted in statistically significant clinical differences between psilocybin and an SSRI in their primary outcomes, had their means of measurement asked about these more nuanced symptoms.

Limitations to psilocybin's therapeutic use

There are several constraints to the therapeutic use of psilocybin. The first is its status as a controlled substance that is heavily restricted as a "Schedule I" drug under US Federal law. This makes it challenging to even research, let alone getting physicians to prescribe it or pharmacies to stock this drug.

Additionally, psilocybin induces mystical and spiritual transformative experiences. As discussed, this appears to be a critical factor in its success as a novel antidepressant; however, this implies that set and setting of drug ingestion are of utmost importance. Without the proper physical and psychological context, psilocybin can actually impede the alleviation of symptoms, as the highest potential for adverse effects occurs under underprepared sets and settings (8).

Successful psilocybin therapy may be dependent on active assistance by a therapist, or "guide" or "sitter" during a psychedelic session. Typically, a patient is allocated two therapists, who are often mental health professionals. The therapists' role is to provide non-directive encouragement and a safe setting to allow unconscious psychological thoughts and emotions to surface. In fact, studies have found that the positivity and strength of the relationship between therapists and patients correlates to the extent and duration of patients' responses (34).

Because of the importance of these therapists and their relationships with patients, it is not a trivial task to compare psilocybin and conventional antidepressants. Unlike SSRIs, for example, psilocybin is not simply taken as a daily prescription; taking psilocybin in the same way one might take an SSRI may not produce comparable antidepressant results.

However, new research in mice suggests that it may be possible to retain the psychological benefits of psilocybin while minimizing alterations in consciousness. Researchers found that psilocybin caused rapid antidepressant effects and alterations in brain connectivity in mice, as it does in humans. However, they were able to reach these benefits without 5-HT_{2A} receptor activation. Activation of this receptor is known to cause alterations in consciousness by all psychedelic drugs and was thought to also cause psilocybin's clinical benefits. This novel research suggests that psilocybin's clinical benefits may be obtained independently of its hallucinogenic effects (35). This finding conflicts with current hypotheses about the essential nature of hallucinogenic experiences contributing to spiritual well-being, so further research on animals and humans is required to corroborate this finding. Without the stigma and complications of psychedelic consciousness-altering experiences, or the necessity to involve 'guides' or 'sitters' in controlled settings, it might be much simpler for doctors to prescribe and for patients to take psilocybin at home.

Microdosing

Another way to potentially circumvent the complications of psychedelic experiences is through microdosing. Most research thus far has focused on the effects of large doses of psilocybin on depression, largely ignoring the phenomena of microdosing. Microdoses are generally defined as being one 10^{th} to 20^{th} of a standard psychedelic dose. Psilocybin's standard dose is 25 mg drug/70 kg body weight. Microdoses are so small that no overt psychedelic effects occur, although the user may still experience alterations in thinking, emotion, and energy levels.

The research that has been done on microdosing and its benefits has found that microdoses of psilocybin have the potential for subtle (positive) cognitive changes, such as convergent and divergent thinking, and effects

on mood. It appears that microdoses can bring about milder versions of the effects of a standard dose without the mind-altering psychedelic experience. However, microdosing's therapeutic value in treating depression is still unclear; there is a pronounced lack of high-quality data available, and results tend not to be as dramatic or effective as one might expect (36), especially when compared to high-dose psilocybin therapy. Nevertheless, this approach still shows promise and requires future investigation.

Conclusion

Depression is a worldwide phenomenon with devastating personal and societal impact and growing worldwide prevalence. This disorder is not well understood, and has been difficult to treat effectively. Current treatments, namely SSRIs, are lacking; they are slow to work and people quickly become tolerant to their effects. In certain cases of depression, SSRIs do not even work at all: patients can become resistant to treatment, and cancer-related depression requires something faster-acting and more experiential. Alternative treatments are clearly needed.

Psilocybin may offer that alternative treatment. Many of the (often misconceived) risks associated with psilocybin, and psychedelics in general, are mitigated simply by being administered in a clinical context with therapists guiding the patient's experience. Emerging evidence that suggests it may be possible to experience psilocybin's antidepressive effects independently of its hallucinogenic effects by dose titration. This may even dispense with the need for 'sitters' or 'guides' and controlled clinical settings and instead, allow self-medication at home. Although both function through 5-HT neurons in the serotonin pathway, SSRIs and psilocybin interact with the brain in very different ways. Psilocybin's (along with all other psychedelics') psychoactive effects are brought about by interactions with the serotonin 5-HT_{2A} receptor, which are usually unaffected by SSRIs. In large doses, the psilocybin user's experience can be transformative, and the experiential aspect alone may be an important factor in psilocybin's significantly greater comparative efficacy as an antidepressant.

Furthermore, the spiritual aspect of psychedelics cannot be overlooked. A major characteristic of cancer-related depression is existential distress, and this symptom is not addressed by conventional antidepressants. It appears psilocybin is able to address it, or at least to a greater extent than conventional antidepressants. This may be related to the experiential factor mentioned above: patients' emotional experiences while using SSRIs and psychedelic drugs are fundamentally different. SSRIs limit limbic responsiveness and promote emotional "blunting" whereas psychedelics place an emphasis on emotional release. These differences in approaches to emotion could be a driving difference between their respective applications as antidepressants (23). Cancer patients can find a previously unreachable existential emotional contentment with this drug in the face of terminal illness, which might greatly improve their quality of life.

Studies show promising results as to psilocybin's applicability as a treatment for depression, especially in instances where conventional treatments are ineffective. Neurologically, these studies found that single doses of psilocybin resulted in previously

unattainable clinical benefits. By seeming to "undo" depression's implications on brain regions such as the prefrontal cortex, amygdala, hippocampus, and global networks, by increasing functional connectivity between high-order DMN, EN and SN brain networks and by equalizing serotonin concentration gradients across cortices, psilocybin therapy allowed people to experience unprecedented antidepressant effects. Psychologically, patients showed reductions in depression, anxiety, and hopelessness, with increases in quality of life and spirituality. It is possible that a single dose of psilocybin may produce psychological benefits lasting up to 8 months. This long duration of effect, combined with the brain's inability to build up tolerance against psilocybin, means the drug could sidestep SSRIs' limitation when it comes to reduced efficacy over time.

Patients with treatment-resistant depression also benefited from psilocybin's subjective emotional effects. Psilocybin allowed them to experience feelings of reconnection and the acceptance of uncomfortable feelings, while previous treatments with SSRIs had perpetuated depression's sense of disconnect and avoidance of painful reflection.

It is important to note that the studies used in this paper are limited by small sample sizes, lack of long-term data, and sample groups that are not representative of every demographic that experiences depression (or even every demographic that experiences treatment-resistant and cancer-related depression). The fact that psilocybin remains illegal in most countries has further restricted research (12). Additionally, the limited number of published studies on this topic, has necessitated referencing nine papers, including six clinical trials, with the same listed author (Robin Carhart-Harris). Different researchers will need to corroborate these findings to confirm their validity.

More robust and abundant research is required to conclusively determine whether psilocybin can offer a viable alternative to conventional antidepressants. A better understanding of the neural basis of depression is needed in order to treat it not only in terms of biomarker concentrations, but in terms of holistic healing; self-report depression tests that ask more nuanced questions are needed in this regard. We need to learn more about psilocybin's mechanisms of action to understand how it brings about its effects, and we need more extensive data to have stronger evidence to draw conclusions. However, preliminary findings show that further research *is* warranted, because of the importance of this issue and from the promising results obtained thus far.

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References

1. Weinberger, A., Gbedemah, M., Martinez, A., Nash, D., Galea, S., & Goodwin, R. (2018). Trends in depression prevalence in the USA from 2005 to 2015: Widening disparities in vulnerable groups. *Psychological Medicine, 48*(8), 1308-1315. https://doi.org/10.1017/S0033291717002781

2. Carhart-Harris, R. L., Bolstridge, M., Rucker, J., Day, C. M. J., Erritzoe, D., Kaelen, M., Bloomfield, M., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Pilling, S., Curran, V. H., & Nutt, D. J. (2016). Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. *The Lancet Psychiatry*, *3*(7), 619–627. https://doi.org/10.1016/s2215-0366(16)30065-7

3. World Health Organization. (2017). *Depression and Other Common Mental Disorders: Global Health Estimates*.

4. Twenge, J. M., & Joiner, T. E. (2020). U.S. Census Bureau-assessed prevalence of anxiety and depressive symptoms in 2019 and during the 2020 COVID-19 pandemic. *Depression and Anxiety*, *37*(10), 954–956. https://doi.org/10.1002/da.23077

5. Yohn, C. N., Gergues, M. M., & Samuels, B. A. (2017). The role of 5-HT receptors in depression. *Molecular Brain*, *10*(1). https://doi.org/10.1186/s13041-017-0306-y

6. Souery, D., Papakostas, G. I., & Trivedi, M. H. (2006). Treatment-resistant depression. *Journal of Clinical Psychiatry*, *67*(SUPPL. 6), 16-22.

7. Carhart-Harris, R. L., Bolstridge, M., Day, C. M. J., Rucker, J., Watts, R., Erritzoe, D. E., Kaelen, M., Giribaldi, B., Bloomfield, M., Pilling, S., Rickard, J. A., Forbes, B., Feilding, A., Taylor, D., Curran, H. V., & Nutt, D. J. (2017). Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. *Psychopharmacology*, *235*(2), 399–408. https://doi.org/10.1007/s00213-017-4771-x

8. Schlag, A. K., Aday, J., Salam, I., Neill, J. C., & Nutt, D. J. (2022). Adverse effects of psychedelics: From anecdotes and misinformation to systematic science. *Journal of Psychopharmacology*, *36*(3), 258–272. https://doi.org/10.1177/02698811211069100

9. Ross, S., Bossis, A., Guss, J., Agin-Liebes, G., Malone, T., Cohen, B., Mennenga, S. E., Belser, A., Kalliontzi, K., Babb, J., Su, Z., Corby, P., & Schmidt, B. L. (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

10. Hastings, R. S., Parsey, R. V., Oquendo, M. A., Arango, V., & Mann, J. J. (2003). Volumetric Analysis of the Prefrontal Cortex, Amygdala, and Hippocampus in Major Depression. *Neuropsychopharmacology*, *29*(5), 952–959. https://doi.org/10.1038/sj.npp.1300371

11. Rosel, P., Arranz, B., Urretavizcaya, M., Oros, M., San, L., & Navarro, M. A. (2004). Altered 5-HT2A and 5-HT4 Postsynaptic Receptors and Their Intracellular Signalling Systems IP₃ and cAMP in Brains from Depressed Violent Suicide Victims. *Neuropsychobiology*, *49*(4), 189–195. https://doi.org/10.1159/000077365

12. Vargas, A. S., Luís, N., Barroso, M., Gallardo, E., & Pereira, L. (2020). Psilocybin as a New Approach to Treat Depression and Anxiety in the Context of Life-Threatening Diseases—A Systematic Review and Meta-Analysis of Clinical Trials. *Biomedicines*, *8*(9), 331. https://doi.org/10.3390/biomedicines8090331

13. Celada, P., Puig, M., Amargós-Bosch, M., Adell, A., & Artigas, F. (2004). The therapeutic role of 5-HT1A and 5-HT2A receptors in depression. *Journal of psychiatry & neuroscience : JPN*, *29*(4), 252–265.

14. Girn M., Roseman L., Bernhardt B., Smallwood J., Carhart-Harris R., Spreng N. (2022). Serotonergic psychedelic drugs LSD and psilocybin reduce the hierarchical differentiation of unimodal and transmodal cortex. *NeuroImage*, 256, 119220, https://doi.org/10.1016/j.neuroimage.2022.119220.

15. Sangkuhl, K., Klein, T. E., & Altman, R. B. (2009). Selective serotonin reuptake inhibitors pathway. *Pharmacogenetics and Genomics*, *19*(11), 907–909. https://doi.org/10.1097/fpc.0b013e32833132cb

16. Pizzagalli, D. A., & Roberts, A. C. (2021). Prefrontal cortex and depression. *Neuropsychopharmacology*, *47*(1), 225–246. https://doi.org/10.1038/s41386-021-01101-7

17. Young, K. D., Zotev, V., Phillips, R., Misaki, M., Drevets, W. C., & Bodurka, J. (2018). Amygdala real-time functional magnetic resonance imaging neurofeedback for major depressive disorder: A review. *Psychiatry and Clinical Neurosciences*, *72*(7), 466–481. https://doi.org/10.1111/pcn.12665

18. Ly, C., Greb A., Cameron, L., Wong, J., Barragan, E., Wilson, P., Burbach, K., Zarandi, S., Sood, A., Paddy, M., Duim, W., Dennis, M., McAllister, K., Ori-McKenney, K.,

Gray, J., Olson, D. (2018). Psychedelics Promote Structural and Functional Neural Plasticity. *Cell Reports*, 23(11), 3170-3182. https://doi.org/10.1016/j.celrep.2018.05.022.

19. Daws, R.E., Timmermann, C., Giribaldi, B., Sexton, J., Wall, M., Erritzoe, D., Roseman, L., Nutt, D., Carhart-Harris, R. (2022). Increased global integration in the brain after psilocybin therapy for depression. *Nat Med,* (28), 844–851. https://doi.org/10.1038/s41591-022-01744-z.

20. Gumnick, J. F., & Nemeroff, C. B. (2000). Problems with currently available antidepressants. *The Journal of Clinical Psychiatry, 61*(Suppl10), 5–15.

21. Wang, S. M., Han, C., Bahk, W. M., Lee, S. J., Patkar, A. A., Masand, P. S., & Pae, C. U. (2018). Addressing the Side Effects of Contemporary Antidepressant Drugs: A Comprehensive Review. *Chonnam Medical Journal*, *54*(2), 101. https://doi.org/10.4068/cmj.2018.54.2.101

22. Talas, A., Cerit, C., & Akpınar Aslan, E. (2018). Comparison of the effects of sertraline and agomelatine on sleep quality, sexual functioning and metabolic parameters in patients with major depressive disorder. *Psychiatry and Clinical Psychopharmacology*, *29*(3), 257–263. https://doi.org/10.1080/24750573.2018.1490096

23. Carhart-Harris, R. L., & Goodwin, G. M. (2017). The Therapeutic Potential of Psychedelic Drugs: Past, Present, and Future. *Neuropsychopharmacology*, *42*(11), 2105–2113. https://doi.org/10.1038/npp.2017.84

24. Kim, K., Che, T., Panova, O., DiBerto, J. F., Lyu, J., Krumm, B. E., Wacker, D., Robertson, M. J., Seven, A. B., Nichols, D. E., Shoichet, B. K., Skiniotis, G., & Roth, B. L. (2020). Structure of a Hallucinogen-Activated Gq-Coupled 5-HT2A Serotonin Receptor. *Cell*, *182*(6), 1574–1588.e19. https://doi.org/10.1016/j.cell.2020.08.024

25. Johnson, M., Richards, W., & Griffiths, R. (2008). Human hallucinogen research: guidelines for safety. *Journal of Psychopharmacology*, *22*(6), 603–620. https://doi.org/10.1177/0269881108093587

26. Baggott, M., Coyle, J., Erowid, E., Erowid, F., & Robertson, L. (2011). Abnormal visual experiences in individuals with histories of hallucinogen use: A web-based questionnaire. *Drug and Alcohol Dependence*, *114*(1), 61–67. https://doi.org/10.1016/j.drugalcdep.2010.09.006

27. Carbonaro, T. M., Bradstreet, M. P., Barrett, F. S., MacLean, K. A., Jesse, R., Johnson, M. W., & Griffiths, R. R. (2016). Survey study of challenging experiences after ingesting

psilocybin mushrooms: Acute and enduring positive and negative consequences. *Journal of Psychopharmacology*, *30*(12), 1268–1278. https://doi.org/10.1177/0269881116662634

28. Watts, R., Day, C., Krzanowski, J., Nutt, D., & Carhart-Harris, R. (2017). Patients' Accounts of Increased "Connectedness" and "Acceptance" After Psilocybin for Treatment-Resistant Depression. *Journal of Humanistic Psychology*, *57*(5), 520–564. https://doi.org/10.1177/0022167817709585

29. Catlow, B. J., Jalloh, A., & Sanchez-Ramos, J. (2016). Hippocampal Neurogenesis. *Neuropathology of Drug Addictions and Substance Misuse*, 821–831. https://doi.org/10.1016/b978-0-12-800212-4.00077-7

30. Lukasiewicz, K., Baker, J., Zuo, Y., and Lu, J. (2021) Serotonergic Psychedelics in Neural Plasticity. *Frontiers in Molecular Neuroscience,* 14:748359. https://doi.org/10.3389/fnmol.2021.748359

31. Carhart-Harris, R. L., Roseman, L., Bolstridge, M., Demetriou, L., Pannekoek, J. N., Wall, M. B., Tanner, M., Kaelen, M., McGonigle, J., Murphy, K., Leech, R., Curran, H. V., & Nutt, D. J. (2017). Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. *Scientific Reports*, *7*(1). https://doi.org/10.1038/s41598-017-13282-7

32. Carhart-Harris, R., Giribaldi, B., Watts, R., Baker-Jones, M., Murphy-Beiner, A., Murphy, R., Martell, J., Blemings, A., Erritzoe, D., & Nutt, D. J. (2021). Trial of Psilocybin versus Escitalopram for Depression. *New England Journal of Medicine*, *384*(15), 1402–1411. https://doi.org/10.1056/nejmoa2032994

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

34. Murphy, R., Kettner, H., Zeifman, R., Giribaldi, B., Kartner, L., Martell, J., Read, T., Murphy-Beiner, A., Baker-Jones, M, Nutt, D., Erritzoe, D., Watts, R., Carhart-Harris, R. (2022). Therapeutic Alliance and Rapport Modulate Responses to Psilocybin Assisted Therapy for Depression. *Frontiers in Pharmacology*, 12:788155. https://doi.org/10.3389/fphar.2021.788155

35. Hesselgrave, N., Troppoli, T., Wulff, A., Cole, A., Thompson, S. (2021). Harnessing psilocybin: antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT2R activation in mice. *PNAS, 118*(17). https://doi.org/10.1073/pnas.2022489118

36. Kuypers, K. (2020). The Therapeutic Potential of Microdosing Psychedelics in Depression. *Therapeutic Advances in Psychopharmacology*, 10, 1-15. https://doi.org/10.1177/2045125320950567.