

Mushrooms, Microdosing, and Mental Illness: The Effect of Psilocybin on Neurotransmitters, Neuroinflammation, and Neuroplasticity

Daniel A Kinderlehrer 

Private Practice, Denver, CO, USA

Correspondence: Daniel A Kinderlehrer, Email kinderlehrer@gmail.com

Abstract: The incidence of mental health disorders is increasing worldwide. While there are multiple factors contributing to this problem, neuroinflammation underlies a significant subset of psychiatric conditions, particularly major depressive and anxiety disorders. Anti-inflammatory interventions have demonstrated benefit in these conditions. Psilocin, the active ingredient of mushrooms in the *Psilocybe* genus, is both a potent serotonin agonist and anti-inflammatory agent, increases neuroplasticity, and decreases overactivity in the default mode network. Studies using hallucinogenic doses of psilocin under the supervision of a therapist/guide have consistently demonstrated benefits to individuals with depression and end-of-life anxiety. Microdosing psilocybin in sub-hallucinogenic doses has also demonstrated benefit in mood disorders, and may offer a safe, less expensive, and more available alternative to full doses of psilocybin for mood disorders, as well as for other medical conditions in which inflammation is the principal pathophysiology.

Keywords: Psilocybin, psilocin, microdose, depression, anxiety, neuroinflammation, anti-inflammatory

Introduction

The incidence of mental health disorders is increasing worldwide, and are a leading cause of disability.¹ Mental illness was more prevalent than heart disease, cancer, and diabetes even before the emergence of the COVID-19 pandemic. This trend was exacerbated by the pandemic, with a significant increase in the prevalence of depression and anxiety disorders in all age groups.^{2,3} Mental health issues have been particularly severe in adolescents: in 2021, the World Health Organization (WHO) reported that 15% of all youth globally suffered from a mental health disorder.⁴ Treatment success of neuropsychiatric disorders varies; current antidepressants have limited efficacy in many patients.⁵ There is clearly a need for more effective interventions.

This review describes the pathophysiology of mental health conditions with an emphasis on the immune dysregulation and neuroinflammation associated with depression and anxiety disorders, and analyzes emerging research that demonstrates the potential of psilocybin to address the physiologic dysregulation associated with mental illness. Psilocybin may offer a safe, therapeutic alternative to the present pharmacopeia.

Stress and Inflammation

For most of the twentieth century, Western medicine subscribed to the tenets of mind-body dualism proposed by René Descartes in the 17th century; namely, that mental phenomena are non-physical, and therefore the mind and body are separate and distinct.⁶ This premise was challenged in 1975 when Robert Ader and Nicholas Cohen at the University of Rochester performed a groundbreaking experiment. They fed rats cyclophosphamide in saccharin-flavored water and documented suppression of immune function. Once the rats were thereby conditioned, they were fed the saccharin-flavored water without cyclophosphamide; the rats again exhibited a decrease in antibody production. Ader and Cohen labeled this observed connection between the brain and immune system “psychoneuroimmunology” (PNI).⁷

Understanding the connection between mind and body has greatly expanded in the ensuing five decades, and with it an appreciation of the bidirectional connectivity between psychological stress and nervous, endocrine, and immune function, referred to as Psycho-Neuro-Endocrine-Immunology (PNEI). Stress leads to stimulation of the sympathetic nervous system (SNS) and activation of the hypothalamic-pituitary-adrenal (HPA) axis. The former leads to the release of catecholamines (CAs) from the adrenal medulla, while the latter leads to the release of glucocorticoids (GCs) from the adrenal cortex. CAs act on adrenergic receptors and GCs act on glucocorticoid receptors; collectively these receptors are expressed on virtually all cells in the body with sweeping consequences. These include the promotion of energy production, suppression of digestive and reproductive function, and modulation of immune function.^{8,9}

However, there is a significant difference in the downstream physiological consequences of stress based on the intensity and duration of the stressor and on individual susceptibility. Acute stress leads to the release of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor- α (TNF- α), with activation of innate and adaptive immune function.⁹ This pro-inflammatory response is tempered by the release of anti-inflammatory cytokines IL-4, IL-10 and IL-13, as well as an increase in circulating cortisol. The sum total impact of acute, short-lived stress in an otherwise healthy, well-resourced individual is immunoprotection.^{8,9}

The same is not true for individuals who are chronically stressed, have underlying health problems, or have a history of prior trauma. In these individuals the impact of stress on immune function leads to unchecked inflammation owing to a multitude of factors. Activation of nuclear factor-kappa B (NF- κ B) leads to maximal transcription of pro-inflammatory cytokines, thereby increasing levels of IL-6 and TNF- α . The release of GCs, while normally anti-inflammatory, can become pro-inflammatory due to decreased GC-receptor levels, amplification of inflammasome NLRP3 activity promoting the release of IL-1 β and IL-18, and increased production of prostaglandin E2 (PGE2). The overall result of chronic stress is an increase in inflammation and the suppression of immune function.^{8–10}

Association of Inflammation with Mental Illness

Inflammation plays a crucial role in the body's response to infection, injury, and tissue damage. Excess inflammation occurs in the setting of chronic psychosocial stress, persistent infection, autoimmune conditions, toxin-induced injury, sleep deprivation, chronic pain, environmental illness, and multiple medical conditions, as well as some competitive and extreme sports. Peripheral inflammation disrupts the blood-brain barrier and leads to activation of glial cells and astrocytes, leading to neurotoxicity and neuroinflammation.¹¹ Chronic neuroinflammation leads to disruption in the central nervous system (CNS) via multiple mechanisms:

- Pro-inflammatory cytokines, including IL-6, TNF- α , and IL-1 β , impact the synthesis, release, and reuptake of multiple neurotransmitters including serotonin, dopamine, and glutamate.¹²
- Pro-inflammatory cytokines activate the kynurenine pathway, depleting tryptophan (the precursor of serotonin), and influencing the regulation of dopamine and glutamate.¹³
- The impact of pro-inflammatory cytokines on neurotransmitters disrupts neurocircuitry in the basal ganglia and anterior cingulate cortex leading to changes in motivation, motor activity, and level of anxiety.¹⁴
- Inflammation is associated with oxidative stress through increased production of reactive oxygen species (ROS). Excessive ROS can result in neurotoxicity and neurodegeneration, negatively impacting neuroplasticity and neurogenesis.¹⁵

There is abundant research documenting the presence of inflammation in patients with mental health disorders. Serum levels of proinflammatory markers including IL-6, IL-1 β , TNF- α , and c-reactive protein (CRP) are higher in subjects with depression than in controls.¹⁶ Likewise, patients with anxiety (increased TNF- α , IL-6, IL-1 β , and CRP¹⁷), bipolar disorder (increased TNF- α , IL-6, and IL-1 β ¹⁸), and psychosis (increased IL-6, IL-10, and CRP¹⁹) exhibit elevated levels of inflammatory markers.

While stress and mood disorders (as well as genetic and environmental factors) predispose individuals to neuroinflammation, the inverse is also true: there is abundant evidence that inflammation can lead to psychiatric illness:

- Administration of pro-inflammatory cytokines IL-1 β or TNF- α to mice and rats results in depressive behavior,²⁰ whereas receptor blockade of TNF- α and IL-6 lead to resilience from stress-induced depression behaviors.²¹
- Injections of *Salmonella typhi* vaccine induced depressive symptoms and psychomotor slowing in neurotypical subjects.²² There are reports of mood disorders and altered mental states including psychosis in association with the administration of different COVID vaccines, allegedly caused by “dysregulated immunomodulation.”²³
- Patients receiving the pro-inflammatory cytokine interferon alpha (IFN- α) for treatment of some cancers and hepatitis B experienced an increased rate of depression and anxiety.²⁴
- There are an extensive number of microbes including bacteria, fungi, viruses and protozoa that are causally linked to mental illness.²⁵ Neuropsychiatric Lyme disease is a prominent example.²⁶
- Children and adolescents with pediatric autoimmune neuropsychiatric disease associated with streptococcal infection/pediatric acute-onset neuropsychiatric syndrome (PANDAS/PANS) suffer from severe mood and behavioral issues in which autoimmune encephalitis is triggered by cross-reactivity to microbial pathogens.²⁷
- Encephalitis associated with antibodies to *N*-methyl-D-aspartate (NMDA) receptors is associated with mental illness including psychosis.²⁸
- Eating disorders, including anorexia nervosa and bulimia, can be caused by infections and autoimmunity.^{29,30}
- Patients with treatment resistant depression (TRD) have higher CRP levels than those who respond to antidepressant medications; greater symptom severity is associated with higher CRP levels.³¹
- There is an increased incidence of depression and other mental health issues in patients with autoimmune illnesses; symptoms of depression in these individuals often respond to immunosuppressive therapy.³²

The bidirectionality of psychosocial stress causing inflammation and inflammation resulting in mental illness is consistent with the continuous cross-talk within the PNEI system.

Anti-Inflammatory Interventions Decrease Severity of Mental Health Disorders

The causal link of neuroinflammation with neuropsychiatric disorders has led to multiple studies evaluating the impact of anti-inflammatory agents in the treatment of these disorders. The majority of these studies investigated the impact of adding an anti-inflammatory agent to an antidepressant compared to a control group who took the antidepressant alone (or with a placebo) in patients with major depression.

Celecoxib is a cyclooxygenase enzyme (COX-2) inhibitor that exerts its anti-inflammatory activity by decreasing the conversion of arachidonic acid to pro-inflammatory prostanoids. Several studies have documented the beneficial impact of adding celecoxib to the psychotropic regimen of patients with TRD, major depressive disorder (MDD), and bipolar affective disorder, resulting in enhanced benefit and increased rates of remission.^{33–42} For example, Halaris et al performed a prospective, controlled double blind study of 47 patients who were taking escitalopram (ESC) but continuing to experience depression. The control group (n=20) received a placebo in addition to the ESC, while the treatment group (n=27) added celecoxib to their ESC regimen. The treatment group “experienced lower depression severity through the entire course of the study, showing significant decrease in depression and anxiety scores as early as week 1.”³³ In most of the clinical studies, sample sizes were small and results were sometimes conflicting. However, meta-analyses have supported the antidepressant impact of adding celecoxib to an antidepressant for the treatment of major depression, although results were not as consistent with bipolar depression.⁴² Other studies have documented that celecoxib alone is effective in the treatment of depression.^{43,44}

Additional trials have explored the role of other anti-inflammatory interventions in patients with mental illness. Statin drugs not only reduce cholesterol via inhibition of HMG-CoA reductase, but are also anti-inflammatory, decreasing the generation of ROS and reducing cytokine release.^{45,46} Multiple studies have documented the increased benefit of adding a statin drug to an antidepressant in the treatment of major depression.^{46–49} It has also been noted that cardiac and post-stroke patients taking statin drugs are less likely to develop depression than those not on statins.^{50–52}

As stated previously, anxiety disorders are also associated with significant inflammation.¹⁷ However, there are few reports examining the impact of anti-inflammatory interventions on anxiety symptoms when not considered as secondary to depression. Hu et al found that aspirin as well as other COX inhibitors decreased anxiety and depression in recently diagnosed cancer patients in a Swedish nationwide cancer study.⁵³ Regarding anti-inflammatory interventions in patients with psychosis, multiple meta-analyses have concluded that anti-inflammatory agents as an add-on therapy improved outcomes in psychotic patients.^{54–57} Thus, the evidence strongly supports the effectiveness of anti-inflammatory agents in many patients with mental health disorders, particularly as add-on therapies in major depression and psychosis.

This review on the impact of microdosed psilocybin on mental health issues will focus on its role in the treatment of depression and anxiety disorders with emphasis on its anti-inflammatory activity and its effect on neurotransmitters.

Psilocybin and Mental Health Disorders

Psilocybin (4-phosphoryloxy-N, N-dimethyltryptamine) is produced by a number of mushrooms in the *Psilocybe* genus. Psilocybin itself is biologically inactive, but after ingestion it is dephosphorylated to the psychoactive alkaloid psilocin (4-Hydroxy-N, N-dimethyltryptamine) by alkaline phosphatases and esterases in the stomach, intestines, kidneys and blood, and rapidly crosses the blood-brain barrier. It is detectable in the bloodstream within 30 minutes of ingestion, reaches peak plasma concentration in two to three hours, and has a half-life of approximately three hours. Psilocin is metabolized via Phase I and Phase II hepatic pathways to form O-glucuronide conjugates that undergo renal excretion.^{58–61}

There is evidence that psilocybin use by humans may predate recorded history, while its use in Mesoamerica for spiritual and occult rituals in the 15th century is well documented. The Swiss chemist Albert Hofmann isolated psilocin from the *Psilocybe Mexicana* mushroom in 1954, and his employer Sandoz distributed this product (along with lysergic acid diethylamide, LSD) to physicians and clinics throughout the globe. During the 1960's there were serious medical investigations into the effect of psilocin on mental health disorders, but in 1971 research was curtailed when it was classified as a Schedule I controlled substance; ie, as having no accepted medical use and with a high potential for abuse.^{58–63}

Over thirty years later, the US Food and Drug Administration (FDA) again permitted research with psilocybin in the treatment of some medical conditions. The bulk of this research has been conducted in controlled settings in which an individual consumes a hallucinogenic dose of the psychedelic substance while under the supervision of a therapist/guide. The resultant “journeys” take approximately four to six hours. In investigative studies to date, subjects have been administered the active metabolite psilocin rather than the whole mushroom.⁶⁴

These studies have consistently demonstrated benefit in patients with TRD, MDD, and anxiety disorders.^{65–72} Terminal cancer patients suffering from psychosocial distress have experienced reduced anxiety, improved mood, and less fear of death.^{73–79} Studies typically employed one or two “journeys”, and benefits were generally sustained and without serious adverse events.⁸⁰ Additional studies have suggested psilocybin's benefit in the treatment of obsessive compulsive disorder (OCD)^{81–85} and addiction syndromes—namely tobacco and alcohol.^{86–92}

The chemical structure of psilocin is similar to serotonin (5-hydroxytryptamine, 5-HT) and is a serotonin agonist. Psilocin binds weakly to a number of serotonin and non-serotonin receptors, but it has a particularly high affinity for the 5-HT_{2A} receptor, which is the most widely expressed serotonin receptor in the body. 5-HT_{2A} receptors are extensively distributed in the brain; the region with the highest concentration of binding sites is the neocortex.^{93–95} There is a high concentration of 5-HT_{2A} receptors in the prefrontal cortex, increasing the structural and functional plasticity of these cells. Activation of this receptor modulates mood, cognition and perception.^{96,97} The significance of psilocin's capacity to bind to the 5-HT_{2A} receptor has been demonstrated in both rats and humans: pre-treatment with ketanserin, a 5-HT_{2A} receptor antagonist, blocks the psychotomimetic action of psilocin.^{93–95,98,99} There is also evidence that activation of 5-HT_{2A} receptors leads to the release of dopamine in the ventral striatum of the basal ganglia as well as glutamate release from pyramidal neurons.^{63,100–104}

Serotonin 5-HT_{2A} receptors have been detected on all major immune-related cells including macrophages, monocytes, and neutrophils. Activation of these receptors has profound anti-inflammatory activity. Stimulation of 5-HT_{2A} receptors blocks TNF- α and IL-1 β activity, inhibits release of IL-6, and suppresses NF- κ B, which is necessary for the maximal transcription of these cytokines.^{63,94,100} Activation of the 5-HT_{2A} receptor with the agonist (R)-2,5-Dimethoxy-4-iodoamphetamine (DOI) in rats has demonstrated robust blockade of TNF- α activity, with reduced expression of cytokines, chemokines, and pro-

inflammatory cell adhesion, including reduction in IL-6.¹⁰⁵ Mason et al studied the immune status of healthy humans after administration of oral psilocybin compared with placebo, and found an immediate reduction in the plasma concentration of TNF- α in the treatment group.¹⁰⁶ Although there was no immediate change in IL-6 and CRP, at seven days these levels were reduced while TNF- α concentrations had returned to baseline. They also documented an association between the degree of reduction of IL-6 and CRP and the positive effect on the participants' mood and social activity.

The evidence is consistent that psilocybin combines the serotonergic, dopaminergic, and glutaminergic effects of antidepressants with potent anti-inflammatory action, thus combining the pharmacologic actions analogous to those found in studies performed with celecoxib or a statin drug and a selective serotonin reuptake inhibitor (SSRI).

Psilocybin's therapeutic potential is likely also related to its ability to promote neuroplasticity. Depression is associated with decreased brain-derived neurotrophic factor (BDNF) with decreased synaptic density and aberrant network function.¹⁰⁷ Antidepressants act by binding to tyrosine kinase receptor 2 (TrkB), the BDNF receptor that promotes neuroplasticity in the prefrontal cortex (PFC).¹⁰⁸ Like ketamine and SSRIs, psilocybin also stimulates TrkB, increasing BDNF and promoting neurogenesis with increased synapse number and function as well enhanced spine density synaptogenesis.^{99,109,110} This action has implications for emotional regulation and the ability to adapt to new cognitive and emotional experiences, and is also dependent on stimulation of the 5-HT_{2A} pathway.⁹⁹

Preliminary studies suggest that higher BDNF levels decrease activity in the default mode network (DMN),¹¹¹ a group of brain regions containing several cortical areas including the medial PFC, posterior cingulate cortex, ventromedial cortex, and angular gyrus, and sub-cortical areas including the hippocampus, amygdala, and the thalamus.¹¹² The DMN is typically active when an individual is in a task free, resting state; eg, during self-referential thinking, rumination, or daydreaming. Anxiety and depressive disorders are associated with abnormal activity of the DMN, which can lead to excessive rumination, negative thought patterns, and impaired emotional regulation.¹¹³ Functional magnetic resonance imaging (fMRI) in subjects on psilocybin have demonstrated decreased activity in the PFC, posterior cingulate cortex, and other DMN regions, resulting in "unrestrained cognition."¹¹⁴ The capacity of psilocybin to reduce excess activity in the DMN may be a significant mechanism whereby psilocybin exerts its long-lasting antidepressant action, allowing relief from negative thought patterns and emotional biases. Reduced DMN activity can result in profound alterations in consciousness and is likely responsible for the mystical-type experiences reported by Griffiths et al, with decreased self-other discrimination and even complete ego dissolution.¹¹⁵ Decreased activity in the subcortical structures of the limbic system suggests that psilocybin may have therapeutic potential in patients with post-traumatic stress disorder (PTSD), as discussed below.

While ketanserin, the 5-HT_{2A} receptor antagonist, blocks the hallucinogenic action of psilocybin, it does not block its antidepressant effect.¹¹² It is apparent that psilocybin mediates actions other than binding to 5-HT_{2A} receptors that positively impact mood. Psilocybin interacts with other serotonin receptors including 5-HT_{1A}, 5-HT_{2B}, and 5-HT_{2C}, which may account for some of its antidepressant action.¹¹⁶ Muir et al have isolated psychedelic responsive neurons in the medial PFC without 5-HT_{2A} receptors that have anxiolytic effects (this study was done in mice with DOI, a serotonergic psychedelic).¹¹⁷ Figure 1 demonstrates the confluence of actions in which psilocybin has known psychedelic and antidepressant action.

Regarding safety, Studerus et al analyzed data on 110 healthy subjects who had received hallucinogenic doses of psilocybin in eight double-blind placebo-controlled studies.⁸⁰ They stated that "All acute adverse drug reactions were successfully managed by providing interpersonal support and did not need psychopharmacological intervention. Follow-up questionnaires indicated no subsequent drug abuse, persisting perception disorders, prolonged psychosis or other long-term impairment of functioning in any of our subjects." Psilocin has a high therapeutic index: it has been estimated that a lethal dose is 500 times a therapeutic dose of up to 30 mg.⁸¹

Microdosing vs Macrodosing

Microdosing is the practice of consuming a low, sub-hallucinogenic dose of psilocybin on a regular basis. It is noteworthy that microdosing was commonly used among the Mazatec people in Mexico "to support the healing of physical conditions and emotional states such as sadness, anger, envy, isolation and agitation."¹¹⁸ In the macrodose studies described above, the average dose of psilocin administered was 25 milligrams (mg), which is roughly equivalent to 5 grams (gm) of whole dried

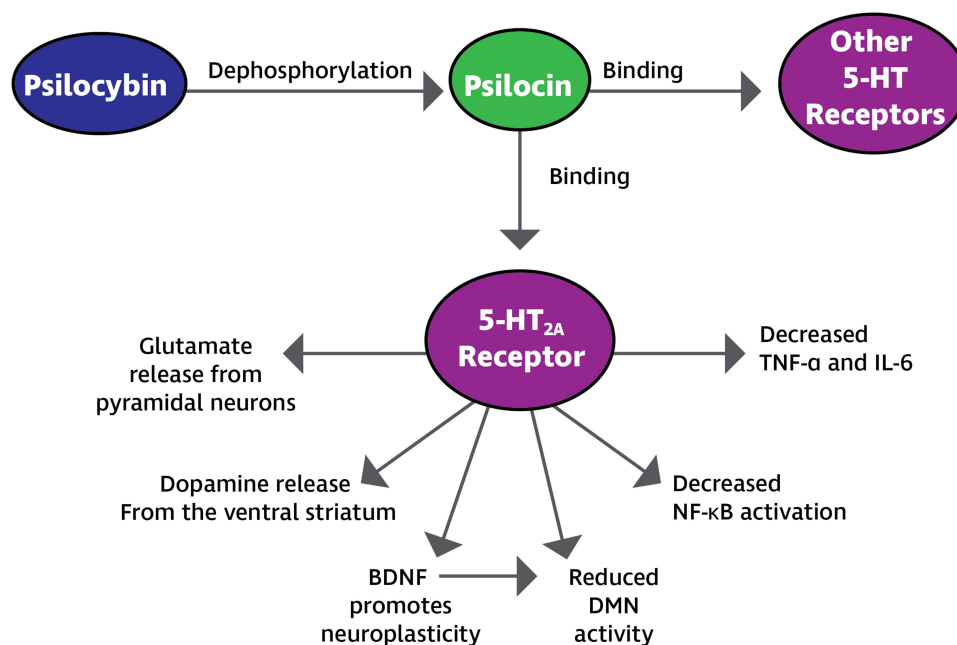


Figure 1 The physiologic mechanisms of psilocybin as a serotonin agonist with an affinity for the 5-HT_{2A} and other 5-HT receptors, whereby psilocybin exerts psychedelic and antidepressant activity.

Abbreviations: 5-HT, 5-hydroxytryptamine; TNF- α , tumor necrosis factor-alpha; IL-6, interleukin-6; NF- κ B, nuclear-factor kappa B; BDNF, brain-derived neurotrophic factor; DMN, default mode network.

mushroom, although potency can vary. The average microdose is 100 to 300 mg of dried mushroom taken in various patterns of alternating days such as three times weekly or four days in succession and three days off.^{118–120}

In general, the intention of microdosing psilocybin is to access similar benefits as with macrodosing, but at more convenience, less cost, and without a hallucinogenic journey or perceptual disturbances. Specific motivations include improving mood and decreasing anxiety, increasing sleep, augmenting cognition, enhancing mindfulness, cultivating empathy and spirituality, stimulating creativity, and decreasing substance use.^{118–120}

Rootman et al compared 4050 microdosers to 4653 non-microdosers to assess the benefits of microdosing.¹¹⁸ Eighty-five percent of respondents were microdosing psilocybin and 15% were microdosing LSD; 39% of those microdosing psilocybin combined it with other substances in a process referred to as stacking, usually adding niacin, chocolate, or lion's mane mushroom, alone or in combination. The two groups were matched for demographics, including histories of substance use and mental health concerns. Among the one-third of each group that reported mental health concerns, the microdose group reported less depression, anxiety, and severity of stress symptoms.

There are few prospective studies on the mental health benefits of microdosing psilocybin that excluded users of LSD. In a follow-up study, Rootman et al did a prospective comparison of 953 psilocybin microdosers with 180 non-microdosers over a 30-day period.¹²¹ The microdose group reported improvements in mood with less anxiety, depression, and stress when compared to the control group. Polito and Stevenson performed a longitudinal study with daily tracking of 98 microdosers over a six-week period.¹²² The investigators were assessing psychological functioning and excluded participants with self-reported mental illness. Nevertheless, participants recorded a significant decrease in depression and stress ratings as well as improvements in attention and focus. Likewise, Kaertner et al performed a longitudinal study in which 81 subjects self-reported increased psychological well-being, emotional stability and reductions in state anxiety and depressive symptoms at the four-week primary endpoint, plus increases in psychological resilience, social connectedness, agreeableness, nature relatedness and aspects of psychological flexibility.¹²³ However, the investigators also found that “positive expectancy scores at baseline predicted subsequent improvements in well-being” and therefore could not rule out a placebo response.

Table 1 Reports Involving Microdosing Psilocybin but Not LSD to Human Subjects

First Author, Year	Study Title	Main Objectives	Main Findings/short Comings
Lyes, et al, 2023 ¹²⁶	Microdosing psilocybin for chronic pain: a case series	Report of 3 cases who managed neuropathic pain with microdoses of psilocybin	"Robust pain relief" with less reliance on other analgesic medications
Kinderlehrer, 2023 ¹²⁰	The effectiveness of microdosed psilocybin in the treatment of neuropsychiatric Lyme disease: a case study	Report of 1 case of treatment resistant depression and anxiety in a patient with poly- microbial tick-borne infections	Dramatic improvement of symptoms within 48 hours despite patient's skepticism
Rootman et al, 2022 ¹²¹	Psilocybin microdosers demonstrate greater observed improvements in mood and mental health at one month relative to non-microdosing controls	A prospective comparison of mental health benefits in 953 microdosers vs.180 non-microdosers over 30 days	Small to medium improvements in mood and mental health in microdosers vs controls
Cavanna et al, 2022 ¹²⁵	Microdosing with psilocybin mushrooms: a double-blind placebo-controlled study	To study short-term effects on well-being, creativity and cognition	There were no discernable subjective effects in the microdosers relative to controls. However, the microdosers took only 2 doses of a high amount (500 mg) over one week—an exceedingly short trial.
Marschall et al, 2022 ¹²⁴	Psilocybin microdosing does not affect emotion-related symptoms and processing: a pre-registered field and lab-based study	To study the effects of microdosing on anxiety, depression, and interoceptive awareness in a 3-week double blind cross-over study	The participants took 7 doses of 700mg of dried <i>Psilocybe</i> mushrooms. There were no consistent benefits. The dose was quite high and the study became unblinded in the second half.

There are two prospective double-blind placebo-controlled studies that evaluated the impact of microdosing psilocybin. Marschall et al performed a crossover study of 96 participants over three weeks and did not find a different impact on symptoms of anxiety or depression in the active vs placebo intake.¹²⁴ Cavanna et al studied 34 subjects who took psilocybin for one week and a placebo for one week separated by a one-week wash-out period.¹²⁵ This study also did not find a clinical difference while microdosing. It should be noted that both the Marschall and Cavanna trials were of short duration; that crossover designs may not be appropriate to study clinical benefits; and that the doses of psilocybin in each investigation (700 mg in the Marschall study and 500 mg in the Cavanna study) were over twice as high as a standard microdose. Also, in the Marschall investigation, the study became unblinded in the second half of the trial.

Lyes et al reported on a series of three subjects suffering from neuropathic pain who experienced significant relief with psilocybin in microdosed quantities.¹²⁶ The author has documented the case of a patient with neuropsychiatric Lyme disease manifesting as TRD and anxiety who had an excellent response to psilocybin in microdosed quantities (100mg three times weekly) despite skepticism on the patient's part.¹²⁰ Table 1 summarizes the reports on microdosing psilocybin but not LSD to human subjects.

Regarding safety, adverse side effects of microdosing psilocybin are uncommon and limited to short-term anxiety, impaired cognition, and physical discomfort. Psilocybin does not show evidence of addiction potential, and in fact is anti-addictive in that daily intake leads to loss of therapeutic benefits.¹²⁷

Discussion

The efficacy of psilocybin taken at hallucinogenic doses under the supervision of a therapist/guide in a controlled setting has clearly been demonstrated to have a profoundly positive impact on TRD, MDD, and anxiety. The evidence regarding the effectiveness of microdosing psilocybin has suggested benefit in these mood disorders, but is not as strong. Alleged benefits are based on self-reporting of subjective symptoms that are difficult to quantify or validate.¹²⁰ There is clearly a need for controlled double-blind research in matched patient populations who suffer from depression and anxiety syndromes. Future research is needed to clarify how well the benefits of macrodosing also occur at microdosed intake.

The FDA and Drug Enforcement Administration (DEA) continue to categorize psilocybin as a Schedule I substance under the Controlled Substance Act, although in 2018 the FDA also designated it as “a breakthrough therapy” for TRD, and in 2019 for MDD.¹²⁸ In addition, in 2024 the FDA granted breakthrough therapy status to CYB003, a psilocybin analogue, in the treatment of MDD.¹²⁹ This designation is applied to drugs that have demonstrated significant improvement over existing treatments in early trials.

Psilocybin appears to be following the same legal trajectory as *Cannabis*, starting with the legalization of medical marijuana in an increasing number of states and subsequent legalization for recreational use. Despite the FDA’s categorization of psilocybin as a Schedule I drug, it has now been decriminalized in multiple cities and two states, Colorado and Oregon.¹³⁰ A study by the RAND corporation in June 2024 estimated that eight million Americans had used psilocybin in 2023.¹³¹

Nevertheless, the reality is that there is limited access to experiencing a “journey” with a trained therapist/guide due to legal constraints, accessibility of trained therapists/guides, and cost. Microdosing represents an inexpensive alternative with much greater availability that may offer similar benefits to macrodosing. The popularity of microdosing is evident in one online forum that was begun in 2013, which included participants microdosing LSD as well as psilocybin; by 2018 there were 40,000 subscribers, and as of May 2024 there were 271,343.¹³² On a platform limited to psilocybin users, there were 129,000 subscribers.¹³³ In the RAND study cited above, 47% of the estimated eight million psilocybin users in 2013 were microdosing.

Despite the well-documented serotonergic and anti-inflammatory actions of psilocybin, as well as its capacity to increase neuroplasticity and decrease activity of the DMN, it is still not clear how psilocybin exerts its antidepressant activity. The above actions of psilocybin are mediated via psilocybin’s strong affinity to the 5-HT_{2A} receptor, but when binding is blocked by ketanserin, psychotomimetic but not antidepressant action is suppressed.¹¹⁶ Perhaps some of psilocybin’s antidepressant effect is mediated by binding to other neurotransmitter receptors. It is likely that additional mechanisms by which psilocybin exerts its antidepressant and anxiolytic activity have yet to be discovered. These mechanistic pathways will be important to elucidate since they will influence the generation of new drugs to address mental health issues.

The anti-inflammatory and antidepressant action of psilocybin has potential benefit for additional mental health conditions. Individuals with post-traumatic stress disorder (PTSD) experience neuro-endocrine activation of the SNS and HPA axis as well as significant inflammation: elevations in IL-1 β , IL-6, IL-17, TNF- α , and CRP, and a decrease in anti-inflammatory cytokines including IL-4 and IL-10 have been documented.^{134–137} Neuroinflammation is likely a significant factor in the ongoing cycle of PTSD symptoms, and anti-inflammatory interventions may have therapeutic potential.¹³⁷ In addition, there is evidence that psilocybin can decrease reactivity of the amygdala, a key structure in threat perception and the generation of emotions.^{138–141} In fact, preliminary studies suggest that full dose psilocybin has therapeutic value in the treatment of PTSD,^{142–144} and the US Department of Veteran Affairs has listed psilocybin as “one exciting area of research” in the treatment of PTSD.¹⁴⁵ Future research should include the impact of microdosed psilocybin in the treatment of PTSD.

Youth with PANS and PANDAS are suffering from autoimmune encephalitis triggered by cross-reactive antibodies to microbial pathogens. Manifestations of severe neuropsychiatric symptoms include OCD, anorexia, tics, mood disorders, and psychosis.¹⁴⁶ Anti-inflammatory interventions including intravenous immunoglobulin (IVIG) have afforded substantial benefit,¹⁴⁷ suggesting that psilocybin may also be effective. Investigations are underway to determine if psilocybin is beneficial in patients with anorexia nervosa.

As delineated in the initial section of this report, stress is a potent trigger of inflammation. This is evident in studies of adults who experienced adverse experiences in childhood. Danese et al found a significant correlation between childhood maltreatment and inflammation in adults as measured by CRP.¹⁴⁸ The Centers for Disease Control and Prevention (CDC) and Kaiser Permanente have pursued an ongoing research project in which they have correlated adverse childhood experiences (ACE) scores with the subsequent development of psychiatric conditions and chronic diseases.¹⁴⁹ The adverse childhood experiences focus on childhood abuse, neglect, and family dysfunction and, not surprisingly, these issues correlate with a significant increase in mental health issues as adults. However, it is particularly noteworthy that ACE scores also correlate with an increase in inflammation, autoimmune illnesses, cardiovascular disease, stroke, pulmonary disease, cancer, liver disease and obesity, as well as premature mortality.^{149–155}

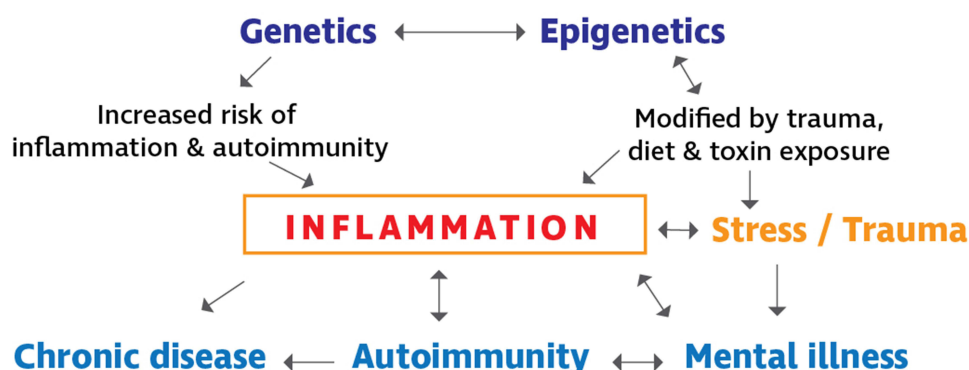


Figure 2 The central role of inflammation in the genesis of mental illness, autoimmunity, and chronic disease. Kinderlehrer DA. Inflammation as the Common Pathophysiology Linking Stress, Mental Illness, Autoimmunity, and Chronic Disease: Implications for Public Health Policy. *J Biomed Res Environ Sci.* 2024;5(3):242–255. Creative Commons.¹³⁶

The common pathophysiology of these conditions is inflammation.^{138,156,157} As summarized by Furman et al:

Recent research has revealed that certain social, environmental and lifestyle factors can promote systemic chronic inflammation (SCI) that can, in turn, lead to several diseases that collectively represent the leading causes of disability and mortality worldwide, such as cardiovascular disease, cancer, diabetes mellitus, chronic kidney disease, non-alcoholic fatty liver disease and autoimmune and neurodegenerative disorders.¹⁵⁶

Additional researchers add Alzheimer’s disease to this list,^{158,159} and several authors have proposed that psilocybin has potential for the treatment of dementia disorders.^{160–163}

Thompson and Szabo described the immune modulating effects of psilocybin and proposed that “Psychedelics hold the potential to attenuate or even resolve autoimmunity by targeting psychosomatic origins, maladaptive chronic stress responses, inflammatory pathways, immune modulation and enteric microbiome populations”.¹⁶⁴

The central role of inflammation in stress, mental health disorders, autoimmunity, and chronic disease is summarized in Figure 2.

Conclusion

Microdosed psilocybin represents a novel and inexpensive anti-inflammatory intervention targeting peripheral- and neuroinflammation without immune suppression. Additionally, psilocybin has potent serotonergic, dopaminergic, and glutaminergic properties, enhances neuroplasticity, and regulates over-activity in the DMN. While it is unclear how well microdosing psilocybin parallels the mental health benefits of full dose psilocybin, it is also possible that microdosing conveys more sustained benefits than single “journeys.” Future research should include not only the impact of microdosed psilocybin on neuropsychiatric conditions, but also its effect on autoimmune diseases and other chronic illnesses associated with inflammation. While its safety in short-term trials has been well documented, future research is also needed to analyze its safety with long-term use.

Abbreviations

WHO, World Health Organization; PN, I psychoneuroimmunology; PNEI, Psycho-Neuro-Endocrine-Immunology; SNS, sympathetic nervous system; HPA, hypothalamic-pituitary-adrenal; CAs, catecholamines; GCs, glucocorticoids; IL, interleukin; TNF- α , tumor necrosis factor-alpha; NF- κ B nuclear factor-kappa B; PGE2, prostaglandin E2; ROS, reactive oxygen species; CRP, c-reactive protein; IFN- α , interferon alpha; PANDAS, pediatric autoimmune neuropsychiatric disease associated with streptococcal infection; PANS, pediatric acute-onset neuropsychiatric syndrome; NMDA, N-methyl-D-aspartate; TRD, treatment resistant depression; COX-2, cyclooxygenase enzyme; MDD, major depressive disorder; ESC, escitalopram; LSD, lysergic acid diethylamide; FDA, Food and Drug Administration; OCD, obsessive compulsive disorder; HT, hydroxytryptophan; DOI, 2.5-Dimethoxy-4-iodoamphetamine; BDNF, brain derived

neurotropic factor; TkrB, tyrosine kinase receptor 2; PFC, prefrontal cortex; SSRI, selective serotonin reuptake inhibitor; DMN, default mode network; fMRI, functional magnetic resonance imaging; PTSD, post-traumatic stress disorder; mg, milligram; gm, gram; IVIG, intravenous immunoglobulin; DEA, Drug Enforcement Administration; CDC, Centers for Disease Control and Prevention; ACE, adverse childhood experiences; SCI, systemic chronic inflammation.

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Disclosure

The author reports no conflicts of interest in this work.

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