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Review

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Dark Classics in Chemical Neuroscience: Psilocybin

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Abstract

Psilocybin is found in a family of mushrooms commonly known as "magic mushrooms" that have been used throughout history to induce hallucinations. In the late 1950s Albert Hofmann, of Sandoz Laboratories, identified and synthesized the psychoactive compounds psilocybin and psilocin which are found in psilocybe mushrooms. Psilocybin was marketed by Sandoz as Indocybin for basic psychopharmacological and therapeutic clinical research. Psilocybin saw a rapid rise in popularity during the 1960s and was classed as a Schedule I drug in 1970. This led to a significant decrease in psilocybin research. Recently, however, preliminary studies with psilocybin have shown promise as potential for the treatment of obsessive compulsive disorder, alcohol addiction, tobacco addiction, major depressive disorder, and the treatment of depression in terminally ill cancer patients. This review describes in detail the synthesis, metabolism, pharmacology, ADRs and importance of psilocybin to neuroscience in the past and present.

Keywords

Psilocybin, Psilocin, Indolealkylamine, Hallucinogen, Psychedelic, Magic mushrooms, Mushrooms, O-acetylpsilocin, Indocybin

I. Intro

Psilocybin (**1**, Figure 1), a tryptamine alkaloid, is found in a family of mushroom-forming fungi that when ingested can cause hallucinations. While found in a variety of mushrooms, the most potent mushrooms are found in the genus *Psilocybe*. The human use of psilocybin dates back from centuries to millennia for medicinal and religious purposes by Mexican Indians. Psilocybin and its most prominent active metabolite, psilocin (**2**), were identified as the psychoactive compounds of their associated Psilocybe mushrooms at Sandoz Laboratories in 1958 by Albert Hofmann.[1] Psilocybin was synthesized by Hofmann in 1959 and later marketed for basic psychopharmacological and therapeutic clinical research by Sandoz as Indocybin. Clinical studies in the 1960s-1970s showed that psilocybin produces an altered state of consciousness with subjective symptoms such as "marked alterations in perception, mood, and thought, changes in experience of time, space, and self."[2] Psilocybin was used in experimental research for the understanding of etiopathogenesis of selective mental disorders and showed psychotherapeutic potential. Psilocybin became increasingly popular as a hallucinogenic recreational drug and was eventually classed as a Schedule I drug in 1970. Fear of psychedelic abuse led to a significant reduction in research being done in this area until the 1990s when human research of psilocybin revived. Today, psilocybin is one of the most widely used psychedelics in human studies due to its relative safety, moderately long active duration, and good absorption in subjects. There still remains strong research and therapeutic potential for psilocybin as recent studies have shown varying degrees of success in neurotic disorders, alcoholism, depression in terminally ill cancer patients, OCD, addiction, anxiety, and even cluster headaches. It could also be useful as a psychosis model for the development of new treatments for psychotic disorders.[3]

The structure of psilocybin, and other indolealkylamine hallucinogens, is similar to the endogenous neurotransmitter serotonin (**3**), the hormone melatonin (**4**), and the hypothesized endogenous psychedelic, *N,N*-dimethyltryptamine (**5**)[4] (Figure 1) all of which are derived from the same parent, tryptamine (**6**).

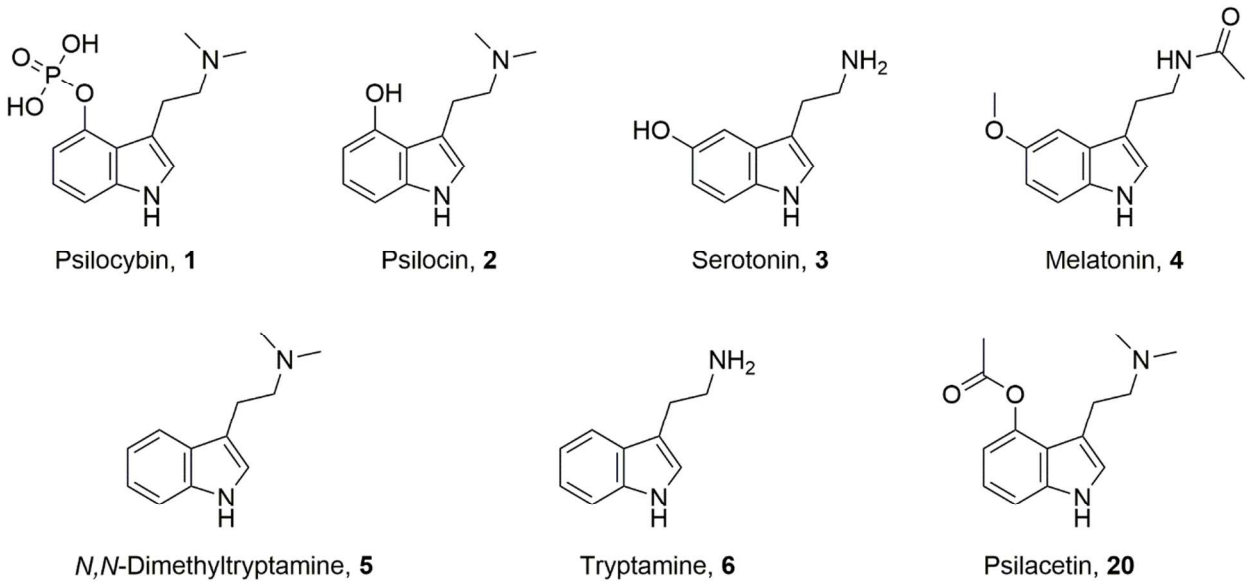


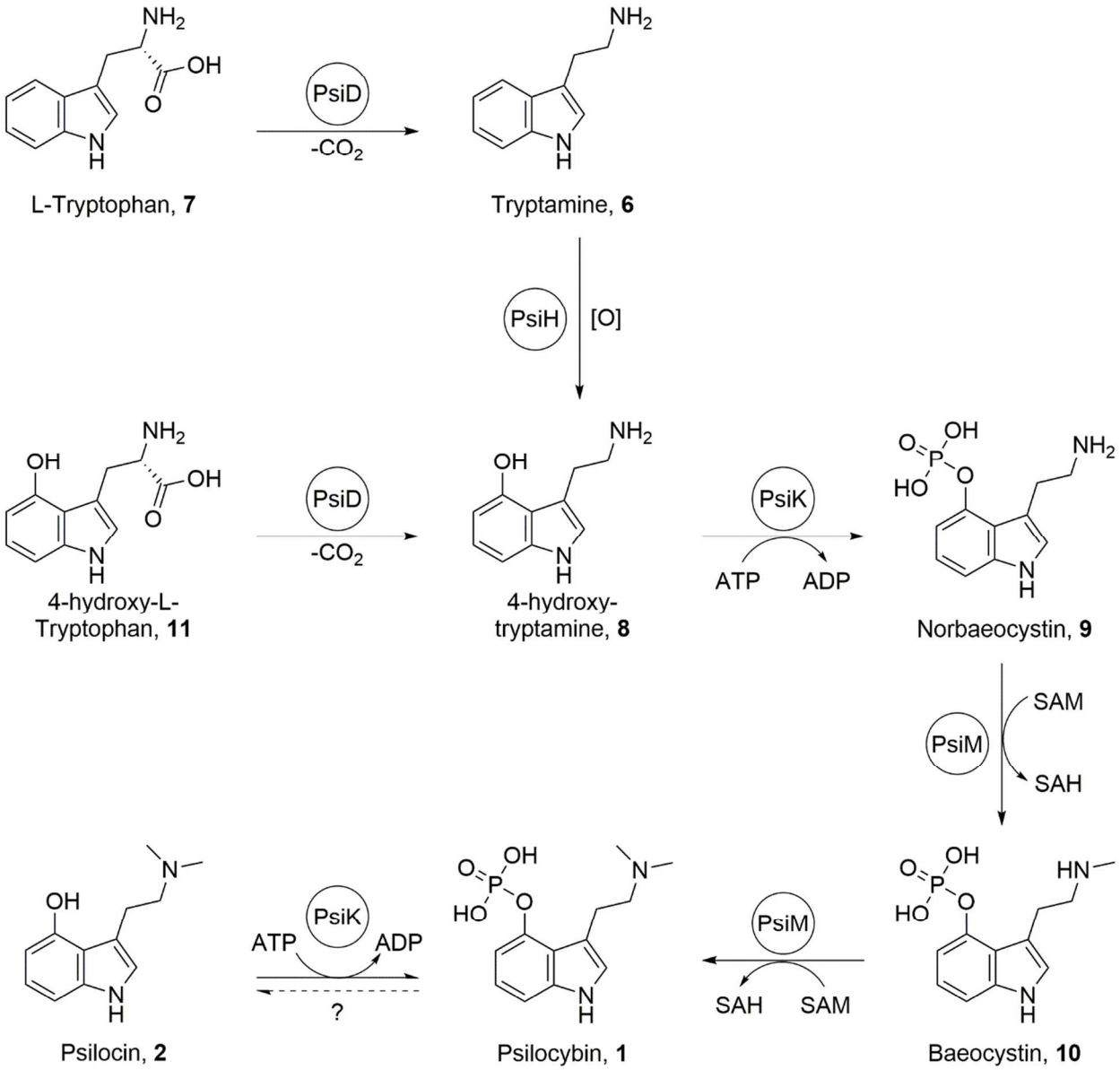
Figure 1: Structure of psilocybin and related compounds

II. Chemical Synthesis

Psilocybin (CAS No.: [520-52-5]) [3-[2-(dimethylamino)ethyl]-1H-indol-4-ol dihydrogen phosphate] [$C_{12}H_{17}N_2O_4P$] [MW = 248.2481 Da] [m.p. = 224 ºC] is a heat labile, water soluble, naturally occurring psychedelic of the indolealkylamine class of hallucinogens that is thought to have very little, if any, activity on its own, primarily acting as a prodrug of psilocin (CAS No.: [520-53-6]) [3-[2-(dimethylamino)ethyl]-1H-indol-4-ol] [$C_{12}H_{16}N_2O$] [MW = 204.268 Da] [m.p. = 174.5 ºC].[4-6] Psilocybin has six hydrogen bond acceptors, three hydrogen bond donors, and a logP of 0.03. It is thought to be unable to freely cross the blood-brain barrier.[7, 8] Psilocybin's metabolite, psilocin, has three hydrogen bond acceptors but only two hydrogen bond donors and

a logP of 1.32, making it significantly more lipophilic than its parent.[4] Thus, psilocin can freely cross the blood-brain barrier to exert its psychoactive effects.[7] The visible difference between these two compounds is easily seen upon inspection, with purified psilocybin forming white, needle-like crystals and purified psilocin forming as an oily, deep brown to black liquid.[4, 6]

The full biosynthetic process used by psilocybin-containing fungi has only recently been identified and is outlined in Scheme 1, below.[9]

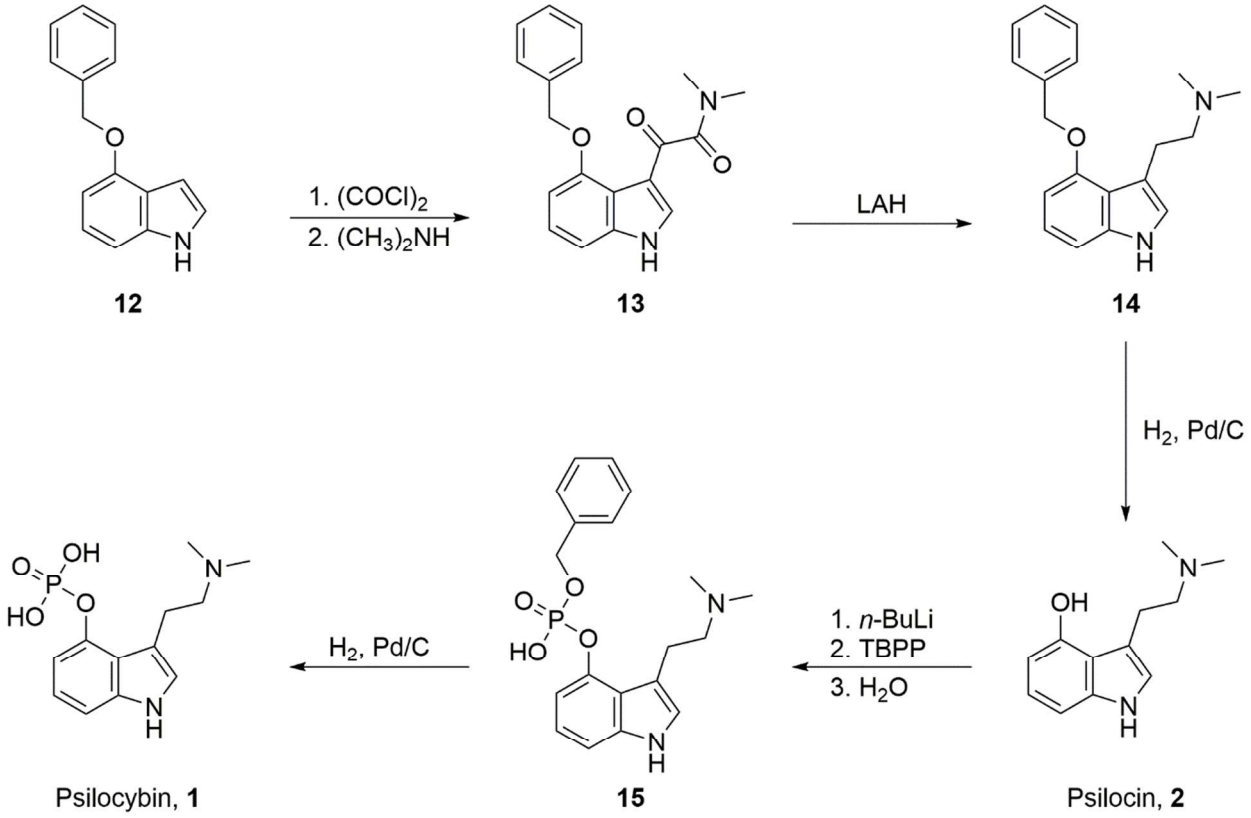


Scheme 1: Biosynthesis of psilocybin[9]

The biosynthetic process begins with tryptophan (**7**), which is decarboxylated to tryptamine (**6**) via the enzyme *PsiD*. Tryptamine (**6**) is then hydroxylated via *PsiH* to form 4-hydroxytryptamine (**8**), which is phosphorylated by *PsiK*, forming norbaeocystin (**9**). Then, *PsiM* methylates norbaeocystin (**9**) to form baeocystin (**10**). Baeocystin (**10**) is then converted into psilocybin (**1**) via methylation by *PsiM*. Psilocybin (**1**) may then reach an equilibrium with psilocin (**2**) via the enzymatic process of *PsiK*.

Alternatively, this biosynthetic process may also begin from 4-hydroxy-L-tryptophan (**11**), which undergoes decarboxylation via *PsiD* to yield 4-hydroxytryptamine (**8**), and the biosynthesis of psilocybin (**1**) continues from this point as outlined above.[9]

Psilocybin may be produced through a completely synthetic process as developed by Albert Hofmann and colleagues at Sandoz Labs (now Novartis). This process is outlined in Scheme 2, below.[1]



Scheme 2: Original synthetic process for the synthesis of psilocybin[1]

The synthesis begins with benzyl protected 4-hydroxyindole (**12**), which is treated with oxalyl chloride and dimethyl amine to give the functionalized indole (**13**). This product is then reduced with lithium aluminum hydride (LAH) in tetrahydrofuran to yield benzyl protected psilocin (**14**). Deprotection under hydrogen gas with palladium on carbon gives psilocin (**2**). This product then undergoes a three-step reaction, first using *n*-butyllithium, followed by tetra-O-benzyl-pyrophosphate (TBPP), and finally water to yield benzyl protected psilocybin (**15**). Debenzylation under hydrogen gas with palladium on carbon gives the final product, psilocybin (**1**).[1] Hofmann's synthesis has since been modified by various chemists who have made numerous contributions to the process to improve overall yield.[10]

III. Drug Metabolism

Once psilocybin (**1**) is ingested, it is absorbed and undergoes hepatic first-pass metabolism where it is rapidly dephosphorylated into psychoactive psilocin (**2**) via an unidentified enzyme (Figure 2). Psilocin enters the systemic circulation and crosses into the brain where it may exert its psychoactive effects.[11, 12] Psilocin undergoes both phase-I and phase-II metabolism. Although primarily phase-II (≥80%), a significant portion still undergoes phase-I reactions.[13] Phase-I metabolism first involves the oxidation of psilocin to 4-hydroxyindole-3-acetaldehyde (**16**) and subsequent oxidation to 4-hydroxyindole-3-acetic acid (**17**) or reduction to 4-hydroxytryptophol (**18**); the enzymes involved in this process have not yet been identified.[11, 12] Phase-II metabolism, via UGT1A10 in the small intestine and UGT1A9 in the liver, results in the formation of a psilocin *O*-glucuronide conjugate (**19**).[12, 14] These metabolites are then renally excreted. A recent study found the elimination half-life of psilocin to be approximately 3 hours (± 1.1 hours) in healthy adults, depending on individual characteristics and route of administration.[15] The complete metabolic pathway of psilocybin has been studied very little and there is still much information that must be gathered to determine the exact mechanisms involved in its metabolism. Figure 2, below, outlines the series of reactions believed to be involved in the metabolism of psilocybin through the analysis of urinary metabolites.[12, 16]

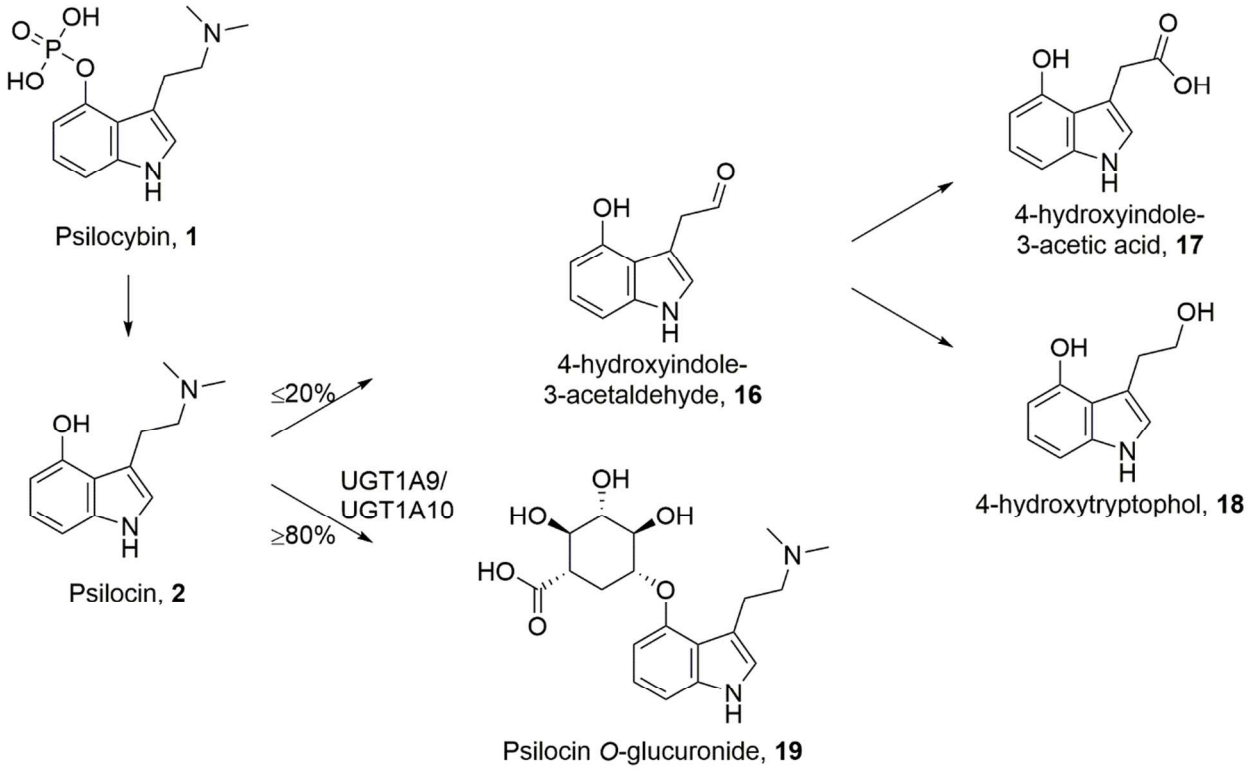


Figure 2: Phase I and phase II metabolites of psilocybin[16]

IV. Manufacturing Information

Psilocybin is classified as a Schedule-I substance in the United States under the Controlled Substances Act of 1971; thus, only limited quantities may be produced each year.[17] Despite its Schedule-I status, psilocybin has been a popular recreational drug since the 1960's and while its use has waned since it became a controlled substance, recreational use continues.[6] Most other developed countries have classified psilocybin and psilocybin-containing mushrooms as illegal as well. The major exception to this generality being The Netherlands, which has a legal loophole allowing the cultivation, sale, and ingestion of psilocybin-containing psychoactive "truffles."[18]

V. Pharmacology, Adverse Reactions, and Dosage

The pharmacology of psilocybin – and psychedelics in general – is poorly understood and highly complex. Psilocybin may have some minor activity of its own; however, it primarily functions as a prodrug for psilocin, which is able to freely cross the blood-brain barrier and exert its psychoactive effects. The major receptor binding sites and associated receptor affinities of psilocin are summarized in Table 1.[19]

Binding Site	K_i (nM)	Binding Site	K_i (nM)
SERT	**3,801**	**α_{1A}**	**>10,000**
5-HT$_{1A}$	**567.4**	**α_{1B}**	**>10,000**
5-HT$_{1B}$	**219.6**	**α_{2A}**	**1,379**
5-HT$_{1D}$	**36.4**	**α_{2B}**	**1,894**
5-HT$_{2A}$	**107.2**	**α_{2C}**	**>10,000**
5-HT$_{2B}$	**4.6**	**β_1**	**>10,000**
5-HT$_{2C}$	**97.3**	**D$_1$**	**>10,000**
5-HT$_3$	**>10,000**	**D$_2$**	**>10,000**
5-HT$_5$	**83.7**	**D$_3$**	**2,645**
5-HT$_6$	**57.0**	**D$_4$**	**>10,000**
5-HT$_7$	**3.5**	**D$_5$**	**>10,000**
H$_1$	**304.6**		

Table 1: K_i of psilocin at major receptors[19]

Psilocin exerts the strongest receptor binding at serotonin receptors -1D, -2B, -2C, -5, -6, and -7 (5-HT$_{1D,2B,2C,5,6,7}$); psilocin has moderate binding potential at serotonin receptors -1A, -1B, and -2A (5-HT$_{1A,1B,2A}$). Additionally, psilocin has activity at histamine-1 (H$_1$) receptors, alpha-2A and -2B ($\alpha_{2A,2B}$) receptors, and dopamine-3 (D$_3$) receptors.[19, 20] It also inhibits the sodium-dependent serotonin transporter (SERT).[19] Deactivation of SERT results in higher

concentrations of serotonin remaining in the synaptic cleft following stimulated serotonin release, allowing repeated firing of serotonergic post-ganglionic neurons.

While the psychoactive properties of psilocin are thought to be primarily due to partial agonism at the 5-HT_{2A} receptor, the pattern of activation of the broad-spectrum of receptors and receptor subtypes is responsible for the unique psychedelic profile seen in users of psilocybin.[21] In the past, there has been some debate about whether 5-HT_{2A} or 5-HT_{2C} receptors or both were responsible for the hallucinations seen in users of psychedelics. Studies have shown that 5-HT_{2A} antagonists inhibit hallucinations in users of psychedelics while 5-HT_{2C} antagonists have not been able to replicate these effects.[22, 23] 5-HT_{2A} receptor agonism is associated with general neuronal excitation, enhanced memory and learning, bronchial and gastric smooth muscle contraction, cardiovascular and gastrointestinal anti-inflammatory effects, and activation results in increased production and release of oxytocin, prolactin, adrenocorticotropic hormone, and renin.[24, 25] The 5-HT_{2C} receptor modulates the activation of proopiomelanocortin (the precursor of α-, β-, and γ-melanocyte stimulating hormone and adrenocorticotropic hormone) and the release of cortisol-releasing hormone. These hormones modulate appetite, insulin sensitivity, glucose homeostasis, and the response to anxiogenic and stressful stimuli.[24]

Psilocin acts as a partial agonist at 5-HT_{1A} receptors, primarily expressed in the dorsal raphe nucleus (DRN), and median raphe nucleus (MRN), located near the midline of the brainstem along its entire rostro-caudal extension, as somatodendritic autoreceptors.[19, 21, 26] The MRN primarily aids in the process of memory consolidation and projects into the hippocampus. The DRN is one of the largest serotonergic nuclei in the human body and provides a significant amount of serotonergic innervation to the forebrain. Additionally, it has some projection into the amygdala and hypothalamus, plays a role in the regulation of the circadian rhythm, and contains

several cell types which function to produce catecholamines and substance-P.[26] Both the DRN and MRN are rich in presynaptic 5-HT_{1A} receptors, and psilocin is 4 to 5 times as potent at presynaptic sites when compared to postsynaptic sites.[19] This preference is due to the large 5-HT_{1A} receptor reserve present on serotonergic raphe cell bodies, a feature not found on postsynaptic cell membranes.[27, 28] When psilocin binds to DRN presynaptic 5-HT_{1A} receptors, it preferentially dampens DRN effects, while leaving downstream cells unaffected and enhancing sympathetic activity associated with the locus coeruleus.[27, 29] Interestingly, although other systems containing 5-HT_{2A} receptors activated by psilocin demonstrated rapid receptor downregulation, 5-HT_{1A} neurons in the DRN were not found to downregulate following the administration of hallucinogens; thus, no tolerance to the inhibitory effects on the DRN by psilocin were seen.[30] It is important to note, that selective 5-HT_{1A} receptor agonists are not hallucinogenic on their own; however, they may play a role in influencing the subtleties of the psychedelic experience.[19] The inhibitory effects seen in the DRN may have implications as to why psilocin seemingly breaks down the usual regulation of neural communication, disrupting connections between some parts of the brain while providing other parts of the brain that have previously never been communicative an opportunity to 'talk'. This effect is sometimes described as a pharmaco-physiological interaction.[31, 32]

Although the dopamine-2 receptor (D_2R) plays a significant role in the hallucinations and delusions seen in psychiatric illnesses, it was hypothesized to have little to do with psilocin's psychoactive effects, and this hypothesis was first confirmed by Vollenweider and colleagues when they found that administering haloperidol, a D_2R antagonist, did not attenuate the psychoactive effects of psilocin.[21, 22] While the dopaminergic effects of psilocin are generally considered to be minimal, it was found to have a relatively high binding capacity at dopamine-3

receptors (D_3R) as compared to other dopamine receptor subtypes. Although the effects exerted through the D_3R remain a mystery, it likely contributes to some of psilocybin's characteristic effects and its ability to mediate addictive tendencies.[24, 29]

A chemically modified psilocin precursor, known as psilacetin (**20**), *O*-acetylpsilocin, or 4-acetoxy-*N*,*N*-dimethyltryptamine, which replaces the phosphoryloxy group found on psilocybin with an acetoxy group, is also readily available. The substituted acetoxy group is believed to be metabolized in an equivalent manner to the phosphoryloxy group, both producing psilocin during first-pass metabolism.[33] This simple modification skirts written laws in the United States when the product is clearly designated "not for human consumption," allowing pseudo-legal import and possession for research purposes only; however, if it were to be used *in-vivo*, the user would be in violation of the Federal Analogue Act.[34] Although psilacetin has been hypothesized to act as an identical pharmacological substitute for psilocybin, many users report a small, yet significant, difference in the effects of each drug.[35] Psilacetin is often described as having a faster onset of action without the anxiety and nausea associated with psilocybin-containing mushroom ingestion (which could be due to avoiding the ingestion of the significant amounts of chitin usually found in these mushrooms) and to have a shorter duration of action with a more peaceful experience throughout, leaving most users with a positive afterglow.[33, 35]

In animals, psilocybin and psilocin are dosed in the range of 0.25-10 mg/kg for behavioral studies. This is a substantially smaller dose than the lethal rat dose of psilocin in fifty percent of a test population (LD_{50}) at 293 mg/kg.[3, 4, 36] While we do not want to infer too much from animal studies, these data suggest a very large therapeutic window and ingesting enough psilocybin-containing mushrooms would be a near impossible feat, considering their ematogenicity.

Tachyphylaxis, the rapid desensitization to a drug or toxin resulting in diminished physiologic effect, is a phenomenon seen with most hallucinogens. Tolerance begins to develop after the administration of a single dose. The mechanism behind this rapid desensitization is the physiologic response to 5-HT_{2A} receptor overstimulation by quickly downregulating receptor sites.[37, 38] In general, it is thought that these receptor sites return to fifty percent of their baseline within three to seven days of the initial dose and return to baseline within one to four weeks, depending on dose and duration of repeated use. Additionally, cross-tolerance is evident between indolealkylamine and phenylalkylamine classes of hallucinogens.[19]

The general effects of psilocybin ingestion are usually dose-dependent in nature and may include physiologic, visual, auditory, cognitive effects, transpersonal, and multi-sensory effects (i.e., synesthesia).[29] There is a significant difference in the effects of low dose and high dose psilocybin. For example, high doses are much more stimulating with significant visual distortion while low doses are mildly sedating with enhanced visual acuity.[29] The physical euphoria or 'body high' is often described as a light, pleasurable tingling sensation that covers the body and provides a feeling of "glowing weightlessness".[29, 39] The range of effects experienced in each of these categories are briefly summarized in Table 2, below.[29, 39]

Commonly Reported Effects of Psilocybin Ingestion	
Physiologic effects	Mild sedation with compulsive yawning; stimulation; physical euphoria; feelings of weightlessness; tactile enhancement; rhinorrhea; mydriasis; hypersalivation; increased systolic pressure; slight elevation in body temperature

Visual effects	Enhancement: color saturation; pattern recognition; visual acuity (at lower doses) Distortions: flowing/breathing/melting of objects and colors; tracers; perspective distortion Hallucinations: bright and colorful shapes and figures seen with eyes closed and with eyes open at higher doses
Cognitive effects	Increased empathy; simultaneous emotions; enhanced objective and situational analysis; music appreciation; ego loss; catharsis; rejuvenation; addiction suppression; time distortion
Auditory effects	Sound enhancement and distortion
Multi-Sensory effects	Synesthesia
Transpersonal effects	Increased spirituality and a sense of interconnection between humanity and a higher power

Table 2: Reported effects of psilocybin ingestion

The full duration of a psilocybin experience is approximately four to seven hours in duration, and normal after-effects are usually dose-dependent and vary anywhere from one to twenty-four hours.[39, 40] Figure 3, below, highlights the average duration and stages of a traditional psilocybin experience.[40]

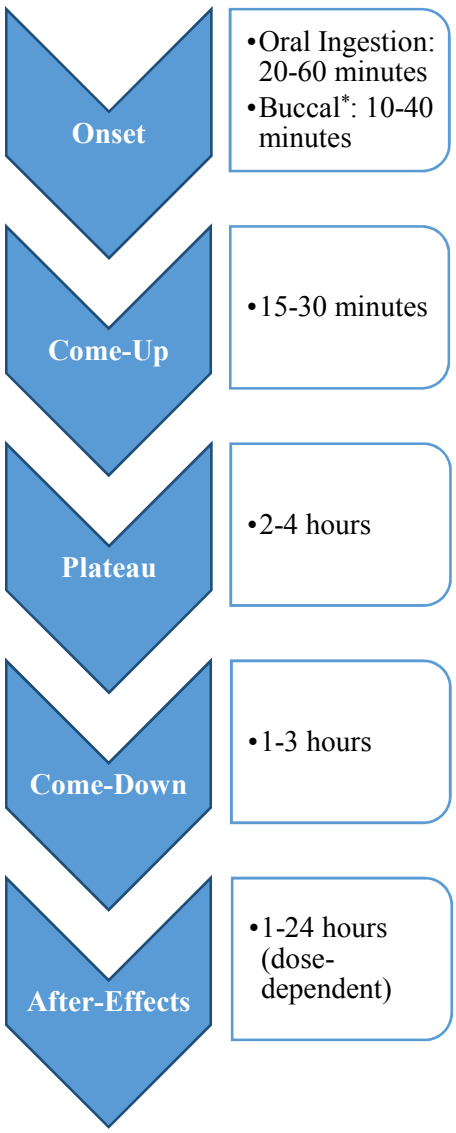


Figure 3: Stages of psilocybin ingestion and effects

**Dried psilocybin-containing mushrooms may be held as a 'quid' between the cheek and gum for a potentially faster onset of action.*

The most common adverse events associated with the ingestion of psilocybin-containing mushrooms are tachycardia, anxiety, nausea, vomiting, diarrhea, emotional lability, delusions, feelings of impending doom, and confusion.[29, 39] Nausea is one of the most common adverse events experienced and is most likely a reaction to ingesting the flesh of the mushroom itself and not directly caused by psilocybin; however, nausea has been reported among studies

administering purified concentrates of psilocybin.[29] More serious adverse events include hallucinogen persisting perception disorder (HPPD), seizures, and a hypothetical risk of a type of cardiac valvulopathy. HPPD is associated with frequent or overly intense psychedelic experiences and causes abrupt 'flashbacks' to a psychedelic experience.[41] The risk of seizures caused by psilocybin ingestion is very low but may be increased in times of heightened physiological stress, including dehydration and extreme fatigue.[8, 42, 43] The concomitant use of tramadol – a mu-opioid receptor agonist with additional serotonin and norepinephrine reuptake inhibitor properties – may increase the risk of seizures due to its innate potential to lower the seizure threshold, which is thought to be primarily caused by its inhibition of the norepinephrine transporter.[44, 45] Damage to the cardiac valves is possible with frequent long-term use due to psilocin's 5-HT_{2B} receptor activity at the heart, which induces the proliferation of cardiac fibroblasts, resulting in a stiffening of the cardiac valves (5-HT_{2B} receptor antagonists are currently under review for the prevention of cardiac remodeling in adults with heart disease).[46, 47] There has been one anecdotal case of a psilocybin-related fatality in a post-heart transplant patient that could have been related to this mechanism.[48] One other potential risk of ingesting psilocybin is the rare incidence of dose-independent intensity. While extremely rare, there have been several anecdotal reports of such cases where the user took a 'light' dose only to progress into a 'heavy' experience.[39]

There has been a common belief that classic psychedelics [i.e., psilocybin, *N,N*-dimethyltryptamine, lysergic acid diethylamide (LSD), and mescaline] increase the risk of psychiatric illnesses, including schizophrenia, and the incidence of attempted suicide. However, several recently published studies dispute these claims, including two large-scale population studies that found no correlation between psychedelic use and mental illness and a 2015 study

that found that individuals who used a classic psychedelic in the past year were 36% less likely to have attempted suicide.[49-51]

The potential for drug-drug, drug-food, or drug-disease interactions with psilocybin is ever present with the limited data available. Some specific drug-drug interactions, however, have been identified through multiple anecdotal reports and probability based on known pharmacodynamic properties. Notably, the most dangerous known drug-drug interaction with psilocybin, which was discussed above, is its interaction with tramadol, which is known to lower the seizure threshold.[44, 45] Synergistic reactions, heightening the psychedelic effects of psilocybin, are to be expected when used in combination with other psychedelics or drugs inhibiting the metabolism of psilocybin (i.e., monoamine oxidase inhibitors).[52] Drugs that do not seem to be synergistic with psilocybin but may alter the course of the experience include caffeine and opioids, which could increase undertones of stimulation or somnolence respectively.[39, 53] Certain drugs that may reduce the effects of psilocybin are ethanol, gamma-hydroxybutyric acid (GHB), selective serotonin reuptake inhibitors (SSRI), and benzodiazepines, the latter of which is often used to abort difficult experiences in a hospital setting.[39, 54]

Two drug-drug interactions which are notable for their unique effects when coadministered with psilocybin are cannabis and amphetamines. When used under the influence of any psychedelic, cannabis can cause relaxation or, in stark contrast, intense anxiety. These variable effects not only seem to differ between individuals but also between experiences. Amphetamines can increase the risk of falling into a ‘thought loop’, (i.e., when a user cannot escape a repetitive set of thoughts or ideas).[39]

VI. History and Importance in Neuroscience

Psilocybin has been found in over 100 species of mushroom, many of which are within the genus *Psilocybe*.[55] The alkaloid psilocybin in the family *Inocybeaceae* appears between 10 to 20 mya, and it is likely that the appearance of psilocybin in the family *Psilocybe* appeared around that time too. Currently species of *Psilocybe* are known in Asia, Australia, United States, Canada, Mexico, Central and South America, Africa, and Europe. There is a great level of evidence that the psilocybin containing species began in Africa and Europe, as well as indication that *Psilocbe* was present in the Old World before the emergence of modern humans.[56]

Psilocybin-containing mushrooms may be found in the wild or grown in a controlled environment from spore prints, which are created by placing the cap of a known mushroom on a sheet of wax paper and allowing the spores to fall onto the paper, creating a unique mushroom 'fingerprint'.[57] While the latter is significantly more common, and much safer, some users still seek 'magic mushrooms' out in the wild. The danger of misidentification is ever present and is an error that even the most experienced mycologists are susceptible to. Misidentification can lead to anything from mild discomfort to death. Abrupt death is most often seen in amateur mycologists searching for psilocybin-containing mushrooms and another type of psychoactive mushroom commonly known as "Fly Agaric" (*Amanita muscaria*), which is the iconic red and white dotted mushroom cap often seen in fairytales (Instead of psilocybin, *A. muscaria* contains the psychoactive drugs muscimol and ibotenic acid.). Unfortunately, several *Amanita* species are deadly, including the aptly named "Death Cap" (*Amanita phalloides*) and "Destroying Angel" (*Amanita virosa*), which can appear very similar to *Amanita muscaria* and related species. [6, 8, 58]

It is argued that the most ancient record of neurotropic mushroom in relation to humanity is in Africa, for the caved walls of the Taaili n'Ajier mountain region of the Sahara Desert contain murals depicting their presence. There is also evidence of cultivation by the ancient

Egyptians from the tomb of Pharaoh Unas and the story of King Cheops and the Magicians. A mural on the wall of a rock shelter, Selva Pascuala, in Spain indicates more prehistoric presence in Europe.[56]

The legacy and use of 'magic mushrooms' is seen throughout early history and continues into the modern era. Early evidence of use by Central and South American shamans has been identified in numerous locations. Modern study began in the late 1950's with ethnomycologist R. Gordon Wasson and continued with famed psychedelic researchers Timothy Leary, Ralph Metzner and Ram Dass at Harvard University, Albert Hofmann at Sandoz Labs, Terrence McKenna, and Jonathan Ott the 1960's and early 1970's. Interest by psychiatrists and psychologists in the 1950s ensued due to its perceived potential as a tool in shortening psychotherapy.[59] Research interested in psychedelic treatment of addiction began as early as the 1950s. Often insightful effects were observed and aided in sobriety, prompting Humphry Osmond, to coin the term "psychedelic" as a way to describe the "mind-manifesting" capabilities of this class of drugs."[55]

Most clinical research was performed in the 1960s, often using the synthetic version Indocybin.[3] Initial work with psychedelic research focused on utilizing hallucinogens to mimic the mental states of schizophrenics or as adjuncts to psychotherapy. Despite the abundance of research during the 1960s, by the 1970s research ended due to societal misuse of psychedelics. Psychedelic substances became illegal with the passing of the *Controlled Substances Act* on May 1st, 1971.[60] There is currently no US federal funding of psilocybin research due to the complexity of the social history behind such psychedelic substances.[55] Due to psilocybin being a Schedule I drug since the 1970s, prohibiting its possession and use, research has been limited.[61] This means

that knowledge in the areas such as metabolic pathway, toxicology, or behavioral safety is lacking.

While illegal, religious use by indigenous peoples must also be taken into consideration, and while certain hallucinogens (i.e., peyote and ayahuasca) have received legal approval specifically for religious use, psilocybin has not. However, many countries maintain a relaxed enforcement policy in areas where psilocybin has cultural significance.

Psilocybin has been found to work for a shorter duration than LSD, produce less anxiety, fewer panicking and affective disturbances, and milder vegetative side effects. This thus makes psilocybin more attractive for research and psychotherapy possibilities.[2] Psilocybin use has been associated with seeking medical treatment but to a very low extent compared to other abused drugs, and the perceived risk of harm is low according to drug experts.[62] These advantages promote psilocybin's research and therapeutic potential.

Two months after a study looking at the mystical-type experiences produced by psilocybin, volunteers rated the experience as having "substantial personal meaning and spiritual significance" as well as found it contributing to sustained positive changes in attitudes and behavior.[63] These observations were also consistent with the ratings by community observers. Sixty-seven percent of the subjects rated the experience to be either the single most or in the top five most meaningful experiences of their life, and some even rated the meaningfulness similar to the birth of a first child or death of a parent. Seventy-nine percent rated it as increasing their current sense of personal well-being or life satisfaction, and the personalities of the subjects were not observed to have been modified.[63]

The recent research that pronounced psilocybin's persisting therapeutic potential from single administration suggests a new area of medicine with psychedelics that "might eventually

alleviate suffering across multiple potential disorders."[55] Preliminary studies of therapeutic use have been positive on safety and tolerability of psilocybin for obsessive compulsive disorder,[64] alcohol addiction,[65] tobacco addiction,[66] and major depressive disorder.[67] In studies of the treatment of depression in terminal cancer patients and treatment resistant depression, researchers found rapid, notable, and lasting anti-anxiety and anti-depressive effects after treatment with psilocybin.[68] In one study of treatment-resistant depression patients, no serious or unexpected adverse effects occurred. Common adverse effects included short term anxiety, confusion or delusion, nausea, and headache, which are previously known expected difficulties from psilocybin. Mild paranoia was presented in one patient, but importantly, no prolonged psychotic symptoms were shown in any of the subjects.[69]

Two studies showed the promising use of a psychedelic like psilocybin to treat late-stage cancer patients with depression and anxiety. Both reported long-term reductions in anxiety and depression, existential distress, and improved quality of life after a single oral dose of psilocybin.[70] A six and a half month follow-up of a study by Ross et al. showed rates at 60-80% for different validated measures of anxiolytic and antidepressant response.[71] A similar study of cancer patients by Griffiths et al. also showed large decreases in clinical and subjective measurements of depression and anxiety. The six month follow up showed prolongation of these changes as 80% continued to show significant decreases in depression and anxiety.[72] Clinical response for both studies were highly correlated with the participants' mystical or spiritual experience. Both studies showed expected adverse effects such as increases in blood pressure, pulse, nausea, vomiting, transient anxiety or occasional rapidly remitted psychotic symptoms; however, both studies showed "improvements in attitudes toward death and the experience of deeply meaningful spiritual experience."[70] Overall this suggests the therapeutic potential of

psilocybin for treatment of depression in cancer patients and the need for further in-depth research.

In a study on the treatment of tobacco addiction with psilocybin, researchers found that the mystical experiences induced were linked to positive changes in behavior, attitudes, values, and increased openness in personality. Eighty percent of participants showed biologically verified seven-day point-prevalence abstinence at 6-month follow up.[66] Furthermore, those successful in abstaining during the 6 months scored significantly higher when measuring their mystical experience. The correlation was significant between tobacco abstinence and level of mystical experience, well-being, as well as personal and spiritual meaning of the psychedelic session. It must be noted, however, that there was no control group created in this study. Forty percent of participants reported at least one challenging experience during the session, such as fear, fear of insanity, or feeling trapped. These instances were readily managed by staff and resolved, providing the case for the need for safe and controlled environments for the clinical use of psilocybin.[73] The 12-month follow-up showed 67% of the participants were biologically verified as abstinent. A follow up 2.5 years after the target quit date showed 75% were abstinent.[55]

In a proof-of-concept study on the treatment of alcoholism via psilocybin, abstinence was increased significantly following administration of psilocybin and was largely maintained at follow-up to 36 weeks.[65] The intensity of the first session was strongly correlated to behavior in the continuation of the study as well as decreases in craving and increases in abstinence self-efficacy. There were no abnormal adverse effects presented. Percent drinking and heavy drinking days decreased during weeks 5-12 relative to baseline and before psilocybin was introduced. Data showed significant improvements in drinking and changes in psychological measures

relevant to drinking. It is also worth mentioning that there was a lack of control group or blinding.[65] More research will be necessary to further investigate psilocybin's efficacy beyond these preliminary observations of addiction.

It should be noted that some studies on the effect of alcoholism remain absent of elements required for confirming causation (i.e. randomization and comparison conditions), and some don't even show statistical significance. This is largely due to the fact that thus far psilocybin studies of addiction have been preliminary and simplified on the basis to confirm safety and see whether the results warrant funding efforts needed for larger randomized clinical trials. Many of these addiction study observations cannot be taken as solid evidence, but they are a suggestion for larger randomized trial and produce considerable therapeutic promise.

The treatment of cancer-related psychiatric distress remains the most advanced research in this area, as favorable results were found in three randomized and controlled trials.[55] Despite these benefits seen and the impact this could have to populations in society, psilocybin is also shown to have its drawbacks.

In a study of 44 patients admitted to a hospital for the ingestion of magic mushrooms, dysphoria was the most common reason for admission to the hospital. The most troublesome feature was found to be short-term alterations in behavior, for some were reported to have become aggressive and violent.[74] Despite low toxicity and low risk of addiction, it can produce acute and rarely persisting adverse psychological reactions. Case reports of non-research use show short-term distressing psychological symptoms have occurred. These symptoms include fear, individuals putting themselves at risk for physical harm, seeking medical help, and enduring negative psychological or psychiatric problems. Putting oneself or others at risk for physical harm was positively correlated with dosage, difficulty of experience, and duration of difficult

experience.[62] Safety issues arise with uncontrolled settings and the unpredictability of the subject response. Carefully controlled settings would improve psilocybin's potential safety.

In a survey of roughly 2000 participants who reported having challenging experiences after ingesting psilocybin mushrooms, 39% reported the experiences as one of the top 5 most challenging experiences of their lifetime. Additionally 11% reported putting themselves or others at risk of physical harm, 2.6% reported having aggressive or violent behavior, and 2.7% reported getting medical help during the "bad trip".[62] The rates and severity of problems from the survey were notably higher than those observed in laboratory research settings that are carefully screened, prepared, and monitored. Overall the survey showed difficult experiences associated with psilocybin as acute psychological distress, dangerous behavior, and enduring psychological problems. Extrinsic factors of a non-laboratory controlled environment can make the experience more difficult and more harmful for those involved. Despite these difficulties, 84% reported having benefited from the experience. The degree of difficulty of the challenging experience as well as personal and spiritual significance and increased life satisfaction were positively correlated.[62] Another large survey demonstrated that increased neuroticism is associated with greater intensity of the challenging experience with psilocybin.[75] It is shown that those with high negative schizotypy typically experience negative and stressful reactions to altered states of consciousness, such as is induced by psilocybin. Even in optimal settings and conditions such as clinical trials, subjects can still face challenging trips. The influence of external environmental confounding factors can make these bad experiences more likely as well as prolonged.[75]

In a study on the immediate and persisting effects of psilocybin, 39% reported that they had an extreme experience of fear, fear of insanity, or feeling trapped during the session, usually during the highest dosage.[63] There was a positive correlation between dosage and ratings of fear

or anxiety, but there was varying onset and duration for each subject. Forty-four percent had delusions or paranoia, again most subjects experiencing this after the highest dose. Generally, there were positive ratings of attitudes on life, attitudes on self, mood, social effects, and behavior following the experience. Despite these challenges, none of the subjects reported feeling a decreased sense of well-being or life satisfaction. None reported bothersome or clinically significant persisting perception phenomena, and there were no reports of future non-study related uses of hallucinogens since. Of those that reached the full criteria for completing a mystical experience, spiritual significance also did not change over time. In fact, 61% rated the two highest doses to be the single most spiritually significant experiences of their lives, 83% rating it in their top five. Eighty-nine percent indicated those sessions increased well-being or life satisfaction and positively changed their behavior at least moderately.[63]

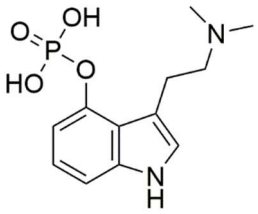
Even if such therapies prove to be effective, the obstacles that come with drug approval are intimidating. Such difficulties include the need for intellectual property protection for old drug developments, high production costs, designing double-blind trials in a drug with evident effects, establishing clinical significance, clinical trial constraints, the need for a site license to possess a Schedule I substance, and the risk pharmaceutical companies would have to undertake. Despite the level of safety psilocybin has proven to exhibit under controlled clinical trials, there is still high risk for its use in less controlled settings, less carefully selected patients, or no dose control.[76]

Those interested in the potential therapeutic and clinical application of psilocybin would have to first take into consideration the efforts necessary to make use of such psychedelic substances possible. However, if future clinical trials continue to show therapeutic promise as well as low adversity of effects, psilocybin could be on the track for regulatory approval for

medical use. If approval is granted, regulations should mirror research studies' screening, preparation, monitoring, and follow-up procedures for efficacy purposes and medical and behavioral risk reduction. [55]

Preliminary studies with psilocybin have shown promise as potential for the treatment of obsessive compulsive disorder,[64] alcohol addiction,[65] tobacco addiction,[66] major depressive disorder,[67] and the treatment of depression in terminally ill cancer patients.[68] In the future psilocybin could be used as a standalone therapy or in combination with other current or future therapies. At present, however, psilocybin remains a widely used, illegal hallucinogen. Psilocybin is truly a dark classic in chemical neuroscience.

Table of Contents Graphic



Psilocybin

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HAG and MGW contributed mainly to the research and draft of the manuscript while RND contributed mainly to editing and rewriting the manuscript.

Conflicts of Interest

The authors declare no competing financial interest.

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