Psilocybin in neuropsychiatry: a review of its pharmacology, safety, and efficacy

Seetal Dodd[1,2,3,4,5]* , Trevor R. Norman[4], Harris A. Eyre[1,2,6,7,8,9,10,11], Stephen M. Stahl[12], Arnie Phillips[1,2], André F. Carvalho[1,2] and Michael Berk[1,2,3,4,5,13]

[1]IMPACT – The Institute for Mental and Physical Health and Clinical Translation, Deakin University, Geelong, VIC, Australia, [2]School of Medicine, Deakin University, Geelong, VIC, Australia, [3]University Hospital Geelong, Barwon Health, Geelong, VIC, Australia, [4]Department of Psychiatry, The University of Melbourne, Parkville, VIC, Australia, [5]Centre for Youth Mental Health, The University of Melbourne, Parkville, VIC, Australia, [6]Neuroscience-Inspired Policy Initiative, Organisation for Economic Co-Operation and Development (OECD), Meadows Mental Health Policy Institute and the PRODEO Institute, Paris, France, [7]Global Brain Health Institute, University of California, San Francisco (UCSF), San Francisco, CA, USA, [8]Global Brain Health Institute, Trinity College Dublin, Dublin, Ireland, [9]Latin American Brain Health (BrainLat), Universidad Adolfo Ibáñez, Santiago, Chile, [10]Brain Health Nexus, Cohen Veterans Network, Boston, MA, USA, [11]Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, TX, USA, [12]Department of Psychiatry, University of California San Diego, San Diego, CA, USA and [13]Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia

Review

Abstract

Psilocybin is a tryptamine alkaloid found in some mushrooms, especially those of the genus *Psilocybe*. Psilocybin has four metabolites including the pharmacologically active primary metabolite psilocin, which readily enters the systemic circulation. The psychoactive effects of psilocin are believed to arise due to the partial agonist effects at the 5HT2A receptor. Psilocin also binds to various other receptor subtypes although the actions of psilocin at other receptors are not fully explored. Psilocybin administered at doses sufficient to cause hallucinogenic experiences has been trialed for addictive disorders, anxiety and depression. This review investigates studies of psilocybin and psilocin and assesses the potential for use of psilocybin and a treatment agent in neuropsychiatry. The potential for harm is also assessed, which may limit the use of psilocybin as a pharmacotherapy. Careful evaluation of the number needed to harm vs the number needed to treat will ultimately justify the potential clinical use of psilocybin. This field needs a responsible pathway forward.

Introduction

Psilocybin is a natural, widely occurring tryptamine alkaloid found in many species of mushroom, most notably those of the genus *Psilocybe*. In addition to psilocybin obtained from mushrooms, synthetic psilocybin and synthetic psilocin is widely available.[1] Psilocybin undergoes metabolism to produce four metabolites. Psilocybin itself is not known to be pharmacologically active and its pharmacological effects are through its primary metabolite psilocin, which is the only metabolite known to be pharmacologically active.

Ritual use of *Psilocybe* mushrooms has an ancient history, as suggested by paleolithic cave paintings in Selva Pascuala, Spain, where mushroom pictographs have been dated to at least 7000 years before present.[2] The best documented example of ritual or ceremonial use of *Psilocybe* mushroom is amongst indigenous populations in Mexico where many sites have been identified. Many populations have traditionally used and continue to use mushrooms that have attained a sacred status.[3] Amongst traditional and current "recreational" users of *Psilocybe* mushrooms, the objective has been to ingest sufficient psilocybin to obtain an altered state of consciousness, described as hallucinogenic or to obtain marked alterations in perception, mood, and thought.[1]

Psilocybin is being investigated as a novel therapeutic agent for potential use in some neuropsychiatric disorders, including mood, anxiety, addictive disorders, and cluster headaches,[1,4] and as an adjunctive pharmacotherapy to assist psychotherapeutic interventions.[5,6] Psychedelics are currently receiving increasing interest from researchers and investors, although several barriers to translating research into clinical practice have been recognized and include the need for clinical supervision of hallucinogenic experiences.[7] Other limitations include drug safety concerns. This review investigates the pharmacology, risks, and benefits of psilocybin and scope the suitability of this agent as a future pharmacological treatment for a multitude of neuropsychiatric conditions.

Pharmacology of psilocybin

Due to its designation as a controlled substance in the USA from 1970, the pharmacology of psilocybin has not been comprehensively investigated and gaps in knowledge remain.[8] Psilocybin itself is not known to be pharmacologically active and the observed effects are mediated by its primary metabolite psilocin (vide infra). Both psilocybin and psilocin are structurally related to the indole alkylamine hallucinogen, *N,N*-dimethyltryptamine, which occurs naturally in a variety of animals and plants.[9] This group of compounds is in turn related chemically to the indoleamine neurotransmitter, serotonin. Psilocybin and psilocin were isolated and purified from the Mexican hallucinogenic fungus *Psilocybe mexicana* by Heim in 1958.[10] Both compounds were chemically synthesized by Hoffman, and the structure was characterized in the same laboratory.[11]

Pharmacokinetics and metabolism

Studies in rodent tissue have suggested complete conversion of psilocybin to psilocin, by loss of the phosphate moiety, before entering the systemic circulation.[17] Thus, studies of the kinetics of the drug are of its major (active) metabolite, psilocin. Indeed, following oral administration of ascending doses of psilocybin, no parent compound was observed in plasma or urine.[15] Few human pharmacokinetic studies have been undertaken so that detailed information of some aspects is unknown. For example, the influence of intrinsic factors on observed pharmacokinetic parameters (eg, hepatic and renal impairment, age, and gender) in addition to that of extrinsic factors are poorly studied, if at all. A summary of the known kinetic studies and their associated parameters for psilocin are presented in Table 1.

Following oral administration of psilocybin, psilocin appears in the plasma within 20 to 30 minutes and maximum concentrations are achieved within 2 to 3 hours of the dose.[15,16] Conversion of the parent compound to psilocin appears to be highly variable based on the dispersion of Tmax values reported in oral administration studies (see Table 1). Maximum concentrations of psilocin were linearly dependent on dose in the only oral ascending dose study conducted to date.[15] Similarly, area under the plasma concentration time curve (AUC) also increased proportionally to the dose confirming linear pharmacokinetics of psilocin in the dose range 0.3 to 0.6 mg/kg.[15]

Psilocin is extensively distributed to the tissues as the apparent volume of distribution exceeds that of total body water.[15] A value of 298 L was determined based on a population pharmacokinetic estimate, assuming a one-compartment model with linear clearance and linear absorption.[15] The model fitted estimate agrees with the volume of distribution calculated from mean published values for AUC and half-life following intravenous administration.[12] In a study of N = 3 human participants, the mean absolute bioavailability of psilocin was 52.7% ($\pm$20.4%) after oral administration[12] which is similar to values determined following administration of ^{14}C labeled psilocybin to rodents.[18]

After oral administration of psilocybin, the apparent terminal elimination half-life of psilocin was variable (see Table 1). An overall mean of 3 ± 1.1 hours was determined after ascending oral doses.[15] Values within a similar range were observed after administration of other oral doses suggesting that elimination half-life is not dependent on the dose, that is, metabolism is not saturated within the dose ranges studied.

Psilocybin is rapidly dephosphorylated after oral administration forming psilocin in the acidic environment of the stomach or by alkaline phosphatase in the intestine and kidney.[19] It has been suggested that psilocybin can be considered a "pro-drug" for psilocin. Psilocin is subject to extensive hepatic first-pass Phase I metabolism by demethylation and oxidation catalyzed by monoamine oxidase and aldehyde dehydrogenase to form 4-hydroxyindole-3-acetic acid (4-HIAA), 4-hydroxy-indole-3-acetaldehyde and 4-hydroxytryptophol.[13,20] None of these metabolites are considered pharmacologically active. Phase II metabolism is catalyzed by the UDP-glucuronosyltransferase (UGT) family of enzymes and is the predominant route of metabolism (>80%).[21] Extensive glucuronidation by UGT1A10 occurs in the small intestine, while UGT1A9 is the main contributor to glucuronidation once absorbed into the circulation.[22] The main urinary metabolite is psilocin-O-glucuronide while 2 to 4% of psilocin is excreted unchanged in the urine.[14] Both the glucuronide of psilocin and 4-HIAA are present in plasma in concentrations far exceeding those of psilocin after oral administration.[12,16] Similarly, the amount of psilocin glucuronide excreted renally has been shown to exceed that of psilocin over 24 hours.[14]

Concentrations of psilocin in plasma show a direct correlation with neocortical 5-HT2A receptor occupancy and subjective psychoactive effects.[23] Single doses of psilocybin from 3 to 30 mg occupied up to 72% of 5-HT2A receptors in a dose dependent manner. The EC50 for receptor occupancy by psilocin was 1.97 μg/L.

Pharmacodynamics

Interaction of psilocin with various receptor subtypes has been determined using radioligand binding studies. An early study showed a rank order of affinity of binding as 5HT2A > 5HT1A > 5HT2B in

Table 1. Pharmacokinetic Parameters for Psilocin Following Administration of Psilocybin

No. of subjects	Dose and route of administration[a]	Cmax μg/L	Tmax	AUC μG H/L	T1/2	References
6	1 mg i.v.	4.8–12.3	85–180 min	1184–2988	106–272 min	Hasler et al[12]
7	0.2 mg/kg p.o.	6–21	70–90 min	20.2–40.8	135 min	Lindenblatt et al[13]
8 (4M, 4F)	212 $\pm$ 25 μg/kg p.o.	N.R.	120–360 min	N.R.	2.59–4.25 h	Hasler et al[14]
12 (10M, 2F)	0.3 mg/kg, p.o.	14.5–17.2	1.15–2.07 h	102–175	2.69 h (1.52–5.49)	Brown et al[15b]
11 (9/2)	0.45 mg/kg, p.o.	22.7–35.1	1.3–3 h	150–261	2.86 h (2.13–18.6)	
10 (8/2)	0.6 mg/kg, p.o.	27.7–43.2	1.55–2.08 h	201–356	3.67 h (2.42–7.71).	
3	25 mg p.o.	19.2 $\pm$ 4.0	140 $\pm$ 46 min	3670 $\pm$ 780	127 $\pm$ 18 min	Kolaczynska et al[16]

[a]i.v. intravenous; p.o. oral.
[b]Study of Brown et al was an ascending dose study in the same subjects. Reduced numbers due to dropouts.

Table 2. Binding Data for Psilocin to Neuronal Receptors and Transporters

SERT	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$	5-HT$_3$	5-HT$_5$	5-HT$_6$	5-HT$_7$	Source
3801	567.4	219.6	36.4	107.2	4.6	97.3	>10^4	83.7	57.0	3.5	PDSP
	190			6.0	410						McKenna et al[24]
6000	123			49		94					Rickli et al[25]
	49			25		10					Blair et al[26]

Note: Ki values expressed as nM. Measured Ki values between studies generally show a lower affinity for 5HT2A than for the other subtypes although there is considerable variation, possibly reflecting different assay conditions, ligands used to define binding sites and tissue preparations and species in which the binding was determined (eg, rat vs human cloned receptors).
Abbreviation: PDSP, NIMH Psychoactive Drug Screening Program.

rat (1A, 2A) or bovine (2B) cortex.[24] Using cell preparations expressing 5HT2A or 5HT2C (rat) or 5HT1A (human) receptors a rank order of binding of psilocin was 5HT2C > 5HT2A > 5HT1A.[26] A later study showed that in addition to binding to 5HT2A receptors psilocin bound to many other receptors, the increasing order of affinity being: 5HT2B, 5HT1D, dopamine D1, 5HT1E, 5HT1A, 5HT5A, 5HT7, 5HT6, D3, 5HT2C, and 5HT1B.[27] Binding to the serotonin transporter (SERT) and the trace amine associated receptor (TAAR1), has also been observed but the significance of binding to this latter receptor for the subjective effects of the drug is not known.[25] Some reported values for psilocin binding to various receptors are shown in Table 2.

Psilocin acts as a partial agonist at the 5HT2A receptor with <40% efficacy (Ca2+ mobilization assay relative to 5HT as a control).[25,28] Intrinsic activity at the 5HT2A receptor (phosphoinositol hydrolysis relative to 5HT) was $52 \pm 5.6\%$.[26] The decrease in the firing rate of the raphe nucleus has been attributed to an agonist effect at 5HT1A autoreceptors.[29] The psychoactive effects of psilocin are believed to arise due to the partial agonist effects at the 5HT2A receptor.[30] However, the 5HT1A receptor has been suggested as a potential mediator of psilocin effects, while effects at 5HT2C receptor seem less likely.[31]

Evidence for the mediation of psilocybin effects by the 5HT2A receptor has been examined using specific antagonists. Thus, pretreatment of subjects with the selective 5HT2 receptor antagonist, ketanserin, dose dependently blocked the perceptual disturbance and hallucinatory phenomena induced by psilocybin (0.25 mg/kg).[32] Furthermore, the atypical antipsychotic, risperidone, but not the typical agent haloperidol, was also able to block the effects suggesting a specific action at the 5HT2A receptor. Administration of ketanserin has been shown to block the effects of psilocybin on mood and emotional face recognition in healthy volunteers[33] as well as sensorimotor gating and controlled (Stroop interference) inhibition processes.[34] These findings are supported by preclinical studies in rodents which show that head twitches and wet dog shakes induced by psilocybin administration are also reversed by 5HT2A antagonists.[35] In addition, some behavioral effects in animals due to psilocybin are prevented by 5HT1A, 5HT2B/2C, and D2 receptor antagonists.[35]

The head twitch response in rodents can reliably distinguish hallucinogenic and nonhallucinogenic 5-HT2A receptor agonists, with positive responses observed for hallucinogenics lysergic acid diethylamid (LSD), psilocybin and mescaline, but not for nonhallucinogenic lisuride.[36]

Psilocin has been associated with changes in neuroplasticity, including neuritogenesis, mediated through tropomyosin receptor kinase B (TrkB), mammalian target of rapamycin (mTOR) and 5HT2A signaling pathways.[37] Neuro-plastogenic effects of psychedelics have been proposed as a nonhallucinogenic mechanism of action that contributes to their therapeutic effect.[38] In addition to 5HT2A receptor-coupled activation of phosphatidylinositol (PI) hydrolysis,[39] 5HT2A antagonism has been shown to activate the TrkB pathway[40] and perhaps other pathways. Biasing the agonism for one vs another pathway (and thus for hallucinogens vs psychoplastic effects in theory) could be the result of numerous mechanisms under current investigation including homomeric vs heteromeric receptor complexes and ligand dependent biased signaling, leading to the prospect that future psilocybin analogues may be able to work at the 5HT2A signaling complex to cause psychoplastic effects without hallucinogenic effects, and thus antidepressant effects without behavioral toxicities.

Systemic administration of psilocin results in alterations of serotonin and dopamine concentrations in specific brain areas of the rat, as demonstrated by in vivo microdialysis.[41] Serotonin was increased in the medial prefrontal cortex but not the nucleus accumbens, whereas dopamine was increased in the accumbens but not the cortex. It was speculated the differential effects could be explained by activation of mesocortical 5HT2A receptors (serotonin increases) and both 5HT1A and 5HT2A activation (dopamine increases) in the accumbens. An increase in endogenous dopamine concentrations was demonstrated in the caudate nucleus and the putamen in healthy volunteers following psilocybin administration, indexed by decreased [^{11}C]raclopride receptor binding potential.[42] Dopamine increases were correlated with euphoria and depersonalisation. Increases in both transmitters thus may explain, at least in part, the mood elevating and psychotomimetic properties associated with psilocybin administration (*vide infra*). These neurochemical changes are accompanied by intracellular and downstream receptor alterations, which have been associated with a proposed mechanism of action of hallucinogens in general.[30] It is suggested that hallucinogenic 5HT2A agonists differentially activate cortical pyramidal neurons resulting in increased expression of (erythroblast transformation-specific related gene) ERG1 and ERG2 and β-arrestin-2.[43,44] Glutamatergic activity in pyramidal neurons of the prefrontal cortex is also increased as a result of 5HT2A activation[30] which in turn leads to interactions of glutamate with AMPA and NMDA receptors on cortical pyramidal neurons. Systemic administration of psilocybin has been shown to increase the production of BDNF in the hippocampus, an effect related to 5HT2A agonist properties.[37,45] Furthermore, the increase in neurogenesis was accompanied by extinction of conditioned fear related behaviors.[45] A complex interplay between serotonergic and glutamatergic systems in the prefrontal circuits may underlie the potential therapeutic effects of psilocin in depressive and anxiety states.

Imaging studies

Different brain imaging modalities have been applied to the study of psilocybin administration in human samples with some

inconsistencies between them. While positron emission tomography (PET) studies have shown that psilocybin causes increased brain activity, other modalities (eg, functional magnetic resonance imaging [fMRI]) have shown decreased activity.[46]

A PET study utilizing glucose metabolism ([18]FDG) showed that 15 to 25 mg of psilocybin increased activity in the prefrontal cortex.[47] In these healthy subjects, glucose uptake was positively correlated with certain psychotic symptoms, in particular ego disintegration. Psilocybin (0.2 mg/kg) increased the metabolic rate of glucose in the right frontotemporal cortical regions, but particularly the right anterior cingulate cortex.[48] Simultaneously, metabolism in the thalamus was decreased. Increases in activity in the left fronto-cortical regions triggered by a cognitive activation task (word association) was blunted by psilocybin.

Magnetoencephalography (MEG) demonstrated reduced spontaneous cortical oscillatory power in the cortical region of male participants (N = 15) who had received an infusion of psilocybin over 60 seconds (2 mg in 10 ml of saline).[49] Elsewhere, global decrease or desynchronization of electroencephalography (EEG) activity was demonstrated in freely moving rats administered psilocin (4 mg/kg).[50]

Resting state fMRI studies have examined the effects of psilocybin on the connectivity between different brain areas and the activity of specific brain regions. The psychedelic experience with psilocybin was suggested to be caused by an impairment of connectivity between different brain regions.[51] Using BOLD imaging, intravenous infusion of psilocybin decreased coupling between the medial prefrontal cortex and the posterior cingulate cortex compared to placebo.[52] It was suggested that the observed alterations in activity and connectivity may be responsible for the subjective effects of the drug. The data from this study were subjected to further analysis to define brain functional networks.[53] A consequence of psilocybin administration was disruption of the normal brain organization and an emergence of strong, long range function connections which are not normally present. This increased integration of cortical regions under psilocybin possibly occurs because of stimulation of 5HT2A receptors. It was speculated that one result of such reinforced cortical connections is the phenomenon of synaesthesia.

Decreased functional connectivity between the right claustrum with the auditory cortex and default mode network (DMN) was demonstrated using BOLD fMRI after psilocybin administration.[54] Concurrently increased connectivity between the right claustrum and the frontoparietal task control network was demonstrated, suggesting a potential role of the claustrum in the therapeutic and subjective effects of psilocybin.

Few neuroimaging studies have examined the effects of psychedelic drugs in patients with psychiatric conditions. An open evaluation of psilocybin was conducted in 19 patients with treatment-resistant depression who underwent BOLD fMRI scanning pre- and posttreatment.[55] Patients received 2 doses of psilocybin (10 and 25 mg) 1 week apart and the post scans were conducted 1 day after the second dose of drug. A main finding was diminished cerebral blood flow in the amygdala posttreatment, which was correlated with decreased depressive symptoms. Resting state functional connectivity in the DMN was increased posttreatment. Response to treatment at a 5-week follow-up was predicted by an increased connection between the prefrontal cortex and the inferior lateral parietal cortex and by diminished para-hippocampal-prefrontal cortex connectivity. In patients with depression, imaging studies have shown a heightened amygdala response to fearful faces which is attenuated by SSRI antidepressants.[56] Examination of

these responses in the same treatment-resistant patients showed increased amygdala reactivity after psilocybin and a reduction in amygdala, prefrontal cortex connectivity.[57,58] These results are at odds with other data which demonstrated a decrease in amygdala reactivity to emotional processing after acute treatment with psilocybin.[59] Furthermore, an increase in the positive mood of healthy volunteers was associated with the decreased reactivity. The differences between studies might simply be due to the investigation of healthy controls vs depressed patients. Also, the proximity of scanning times to the administration of drug might also be a factor (immediately after drug administration vs a delay of 24 hours).

A recent study of people with depression who were treated with psilocybin (25 mg) used fMRI at baseline and 3 weeks posttreatment to find enduring changes in increased global integration of brain networks. Brain networks became more functionally interconnected and flexible after psilocybin treatment.[60] Previous research had associated depressive illness with reduced global integration of brain networks and the current finding suggests a possible mechanism for symptomatic improvement with psilocybin treatment.

Drug safety

Psilocybin and psilocin are considered to have a low potential for acute toxicity due to overdose. A study investigating lethal toxicity in rodents as well as human effects concluded that psilocybin has a high therapeutic index, with a therapeutic dose at 15 to 30 mg and a lethal dose 500 times greater at 6 g.[61] For recreational users, consuming psilocybe mushrooms to a lethal dose is nearly impossible to achieve and lethality is more likely due to misidentification of mushrooms or disrupted judgment or behavior consequent to psychosis or dissociation.[62]

Psilocybin and has long been known to be able to induce symptoms resembling, to some extent, those presented by schizophrenia or psychosis, but with a greater visual effects such as bright and colorful shapes and figures,[1] which appears to be mediated by serotonin type 2 agonism.[32] Concordant with this there is preclinical evidence that psilocybin has an impact on prepulse inhibition.[63]

Adverse effects for psilocybin, psilocin or psilocybe mushrooms include; tachycardia, anxiety, nausea, vomiting, diarrhea, emotional lability, delusions, feelings of impending doom and confusion,[1] dysphoria, derealisation, depersonalisation, and mydriasis.[64] Seizure threshold lowering has been suggested as an adverse effect,[1] but has not been well established.[65] Gastro-intestinal effects are more common with mushroom ingestion and may result from other components in the mushroom preparations.

Of concern, an ongoing condition called hallucinogen persisting perception disorder (HPPD) has been described amongst users of hallucinogenic substances following cessation of use, characterized by flashbacks and ongoing hallucinations of varying intensity.[1] HPPD symptoms include geometric hallucinations, false perceptions of movement in the peripheral visual fields, flashes of color, intensified colors, trails of images of moving objects (palinopsia), positive afterimages, halos around objects, macropsia and micropsia.[66] HPPD has been reported in a recreational user of psilocybin, where alcohol and cannabis use were also present.[67] A study of data from 21 967 people who reported lifetime hallucinogen use suggested that HPPD was rare and that an association between hallucinogen use and adverse mental health outcomes was not found.[68] Elsewhere it was suggested that chronic visual disturbances in

hallucinogen users may be more common, affecting up to 50% of users, with HPPD a less common severe form.[69]

Adverse outcomes may result from "bad trips" including a reported fatal outcome.[70] In the research environment hallucinogenic experiences are generally supported by experienced psychologists with research participants who have been carefully screened and prepared. "Bad trips" may be more common in a recreational drug use environment and it is not clear how common they would be in a routine clinical environment. In a research environment, participants administration and dosage is tightly controlled, which is less so in a routine clinical environment and even less so in a recreational environment. Given the widespread enthusiasm for this class of agent and the equally widespread recreational use, the boundaries between clinical and recreational use are likely to become rapidly very blurry.

Investigations in humans and animals

Recently, there has been a growing interest that psilocybin may be an efficacious drug as an agent for drug assisted psychotherapy and as a psychotherapeutic adjunct for the treatment of addictive disorders, anxiety and depression. Moreover, there is a suggestion that clinical usefulness may be a class effect across psychedelics.[71] However, the safety and tolerability profiles as well as other pharmacological characteristics varies significantly between agents and clinical benefit remains under investigation, suggesting that further work is required.

Animal studies

A single administration of psilocybin (1 mg/kg IP) compared to saline (IP) produced antidepressant-like effects in in the forced swim test and anxiolytic-like effects in the elevated plus maze.[72] Psilocybin "microdosing" has been investigated in a study of rats dosed 0.03 to 10 mg/kg, with presumed serotonin mediated antidepressant-like behaviors reported for doses 0.3 mg/kg and above.[73] Anxiolytic efficacy was not supported in a study of psilocin microdosing (0.05 or 0.075 mg/kg) of rats in the elevated plus maze.[74] Elsewhere, psilocybin (1, 2.5, and 10 mg/kg) did not reduce relapse behavior in a rodent model of alcohol relapse.[75]

Human studies

Improvement in symptoms of mood and anxiety have been reported in three small pilot randomized clinical trials (RCTs) of people with cancer treated with psilocybin. In an RCT with a cross-over design, 12 people with end-stage cancer and anxiety were administered single dose psilocybin (0.2 mg/kg) or placebo (niacin). Psilocybin treatment was well tolerated and associated with improvement on the State–Trait Anxiety Inventory trait anxiety subscale (STAI-anxiety) at 1 and 3 months posttreatment and the Beck Depression Inventory (BDI) at 6 months posttreatment.[76] Elsewhere, an RCT with a similar design randomized 29 people with cancer-related anxiety and depression to single dose psilocybin (0.3 mg/kg) or placebo (niacin), with cross-over at week 7. The psilocybin first group, but not the placebo first group, demonstrated significant within-group reductions (compared to baseline at each post-baseline assessment point) in anxiety and depression after receiving psilocybin and prior to cross over. At 6.5 months post (after both groups received psilocybin), antidepressant or anxiolytic response rates were approximately 60 to 80% measured

with the Hospital Anxiety and Depression Scale (HADS) and the BDI.[77] A larger RCT of people with cancer, randomized participants to low dose first (n = 27; 1 or 3 mg/70 kg) or high dose first (n = 29; 22 or 30 mg/70 kg) of psilocybin in a cross-over design with 5 weeks between treatment sessions and a 6 month follow-up. Data from at least one session was collected from 51 participants, with 46 participants providing 6 month follow-up data. High dose first was superior to low dose first following the first treatment session and second dose was superior to first dose for low dose first following the second treatment session for measures of depression (Hamilton Rating Scale for Depression [HAMD], BDI, HADS) and anxiety (Hamilton Rating Scale for Anxiety [HAM-A], STAI-anxiety), and lower measures of depression and anxiety were sustained as 6 month follow-up for both groups.[78]

Psilocybin was superior to being randomized to a waiting list in a trial of people with major depressive disorder (N = 27) in a trial of two therapist supported psilocybin sessions (20 mg/70 kg in session 1 and 30 mg/70 kg in session 2), with reduction in HAMD and QIDS-SR-16 scores reported from week 1 to week 4 posttreatment.[79] Wait list is a problematic control as it tends to inflate effect sizes and may even serve as a nocebo condition.[80] A meta-analysis of all studies where psilocybin was administered to people with elevated symptoms of depression and/or anxiety identified four studies and found a large effect size for psilocybin treatment for anxiety (Hedges' $g = 1.38$) and depression (Hedges' $g = 1.47$), but suggested problems with detection bias due to inadequate blinding and attrition bias.[81] More recently, an RCT randomized participants with moderate to severe depression (HAMD ≥ 17 at baseline) to receive two separate doses of 25 mg of psilocybin 3 weeks apart plus 6 weeks of daily placebo (psilocybin group, N = 30) or two separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram group, N = 29), plus psychological support. Improvement in depression symptoms using the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) was observed in both treatment groups at 6 weeks posttreatment. In the psilocybin group 21 of 30 participants responded and 17 of 30 participants remitted (response defined as a reduction in QIDS-SR-16 of >50% and remission defined as a score of ≤5) whereas in the escitalopram group 14 of 29 participants responded and 8 of 29 participants remitted, however, the differences in QIDS-SR-16 scores were not significant between groups.[82] This trial is subject to similar issues regarding blinding and expectancy noted above. A larger, multisite RCT of psilocybin for depression is currently in progress (ClinicalTrials.gov Identifier: NCT03866174) with no results available to date.

Psilocybin with psychological support has been investigated in an open-labeled trial of patients (N = 20) with treatment-resistant depression (TRD) who received two doses (10 and 25 mg) 7 days apart. Participants were followed for 6 months and reported reductions in depressive symptoms measured using the QIDS-SR-16 at all posttreatment time points with the greatest improvement at 5-weeks posttreatment.[83]

Psychological interventions assisted by psychedelic drugs has used psycholytic and psychedelic paradigms. Psycholytic approaches are associated with psychoanalytic practice and use low dose psychedelic drugs, especially LSD, to putatively reduce psychological defenses and to release unconscious information, whereas psychedelic approaches integrate the psychedelic experience into the psychotherapy session.[84] Psilocybin has been used for psychedelic assisted psychotherapy.

Psilocybin assisted psychotherapy, where psilocybin treatment is adjunctive therapy to enhance a psychotherapeutic intervention

was first studied from 1961 in the context of recidivism in prison inmates released on parole, where incarcerated prisoners nearing their parole dates were offered sessions using psilocybin in addition to session(s) that did not include medications. Despite initial, possibly falsified reports of strong antirecidivist effects more recent reanalyses of the original data suggests that effects were modest and not statistically significant.[85]

Some evidence for efficacy of psilocybin assisted psychotherapy to treat substance use disorders was demonstrated from small open labeled trials for tobacco smoking cessation and alcohol cessation. An open-labeled pilot study (N = 15) included three sessions with moderate (20 mg/70 kg) and high (30 mg/70 kg) doses of psilocybin administration occurring in weeks 5, 7, and 13 within a 15-week course of smoking cessation treatment. Twelve of 15 participants were abstinent from smoking (confirmed by exhaled carbon monoxide and urinary cotinine) at the 6-month follow-up, however the study design does not permit discerning the contribution of the psilocybin sessions to the smoking cessation rate.[86] Elsewhere, psilocybin sessions at 4 (0.3 mg/kg) and 8 (0.4 mg/kg) weeks were included in a 12 week program of 14 sessions of psychosocial treatment for alcohol dependence (N = 10). Compared to baseline, significant reduction in percent heavy drinking days and percent drinking days was observed at weeks 5 to 12 of treatment and remained low until the final follow-up visit at week 36 for the nine participants that completed all assessments.[87]

It is unclear from the available research designs if concomitant administration of psilocybin amplifies the benefits of psychotherapy or whether benefits, if present, are driven by either of the elements alone. Multi arm studies disentangling these variables are necessary to provide the requisite clarity. A further methodological issue that needs to be resolved is that many psychotherapy trials involve considerable face to face contact, support, and reinforcement. It is known that nonspecific therapeutic benefits are robustly associated with the quantity and enthusiasm of the available clinical support and the next generation of trials needs to ensure that these elements are matched between treatment arms.

Psilocybin microdosing has not been found to be effective. A study of psilocybin microdose vs placebo for well-being and cognition in volunteers (N = 191) demonstrated improvement from baseline in both study arms, suggesting that improvement could be attributed to the placebo effect.[88]

Human studies are summarized in Table 3 and the mechanism of action of psilocybin is described in Figure 1.

Discussion

Psilocybin has been used by several cultures for millennia, suggesting a historical experience-based knowledge of its use. Its use in traditional rituals has been documented where it has been consumed to induce altered states of consciousness often as religious or mystical experiences. However, there is little evidence of the traditional use of psilocybin containing mushrooms as treatment for medical or neuropsychiatric illness, rather psilocybin mushrooms have been sought specifically for their hallucinogenic properties. The modern pharmacopeia has many examples of pharmaceuticals

Table 3. Clinical Trials of Psilocybin for Neuropsychiatric Disorders

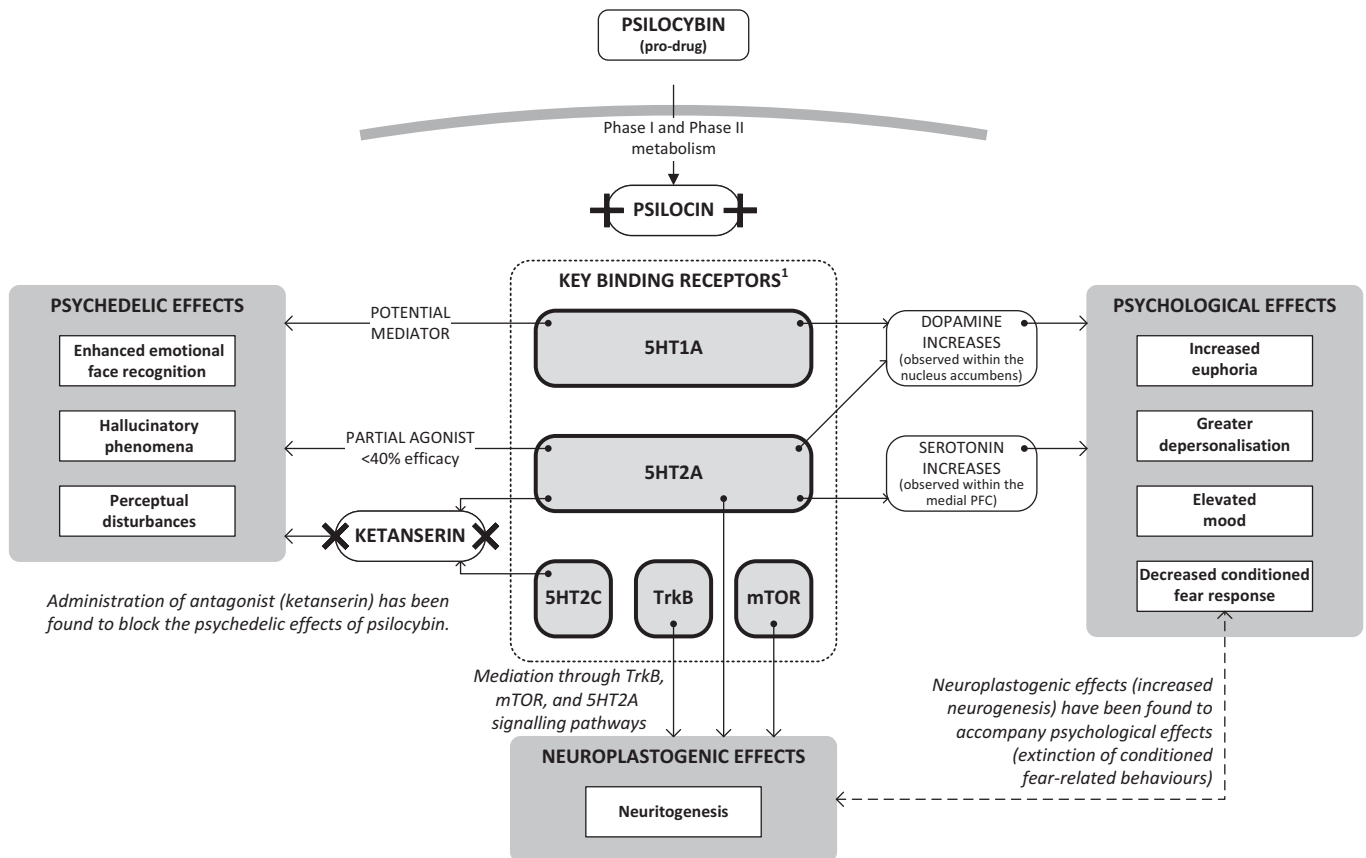| Treatment	Cohort	Study design	Outcomes	References
Psilocybin (0.2 mg/kg oral) or placebo (niacin)	Advanced stage cancer (N = 12)	Randomized, placebo controlled trial	Nonsignificant trend to decreased depression and anxiety	Grob et al[76]
Psilocybin (22 or 30 mg/70 kg oral) or low dose psilocybin (<1 or 3 mg/70 kg oral)	Advanced stage cancer and mood or anxiety disorder (N = 51)	Cross-over (5 week separation between sessions)	Decreased depression and anxiety sustained at 6 month follow-up	Griffiths et al[78]
Psilocybin (0.3 mg/kg oral) or placebo (niacin)	Advanced stage cancer (N = 29)	Cross-over (7 week separation between sessions)	Decreased depression and anxiety sustained at 6 month follow-up	Ross et al[77]
Two oral doses of psilocybin, 10 and 25 mg, 7 days apart in a supportive setting	Severe, unipolar, treatment-resistant major depression (N = 26)	Open-labeled trial	Reductions in depressive symptoms sustained at 6 month follow-up. Greater benefit predicted by the quality of the acute psychedelic experience	Carhart-Harris et al[83]
Two psilocybin sessions (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg), plus supportive psychotherapy	Major Depressive Disorder (N = 27)	Randomized, 8 week waiting list-controlled clinical trial	Reductions in depressive symptoms	Davis et al[79]
Psilocybin (2 × 25 mg doses 3 weeks apart) plus 6 weeks of daily placebo (psilocybin group) or Psilocybin (2 × 1 mg doses 3 weeks apart) plus 6 weeks of daily oral escitalopram (escitalopram group)	Long-standing, moderate-to-severe major depressive disorder (N = 59)	Randomized, controlled trial	Psilocybin equivalent to escitalopram for reductions in depressive symptoms	Carhart-Harris et al[82]
Psilocybin (20 and 30 mg/70 kg, 2-3 doses) with cognitive behavioral therapy for smoking cessation	Tobacco smoking cessation (N = 15)	Open-labeled trial	10 participants (67%) were confirmed as smoking abstinent at 12-month follow-up	Johnson et al[86]
Psilocybin (sessions at 4 (0.3 mg/kg) and 8 (0.4 mg/kg) weeks) were included in a 12 week program of 14 sessions of psychosocial treatment for alcohol dependence	Alcohol dependence (N = 10)	Open-labeled trial	Increase in abstinence with intensity of effects in the first psilocybin session (at week 4) strongly predicting change in drinking during weeks 5–8	Bogenschutz et al[87]

Figure 1. Mechanism of action for psilocybin, describing the psychedelic, psychological, and neuroplastogenic effects.
Note: 1. Additional binding receptors include: 5HT2B, 5HT1D, dopamine D1, 5HT1E, 5HT1A, 5HT5A, 5HT7, 5HT6, D3, 5HT2C, 5HT1B, SERT, and TAARI. Reported values for psilocin binding to various receptors are shown in Table 2.

that were discovered by investigating traditional plant-based remedies, although typically there has been some level of overlap between the traditional use and the modern indication for use or sought mechanism of action.

In healthy humans, psilocybin use is associated with increased emotional empathy[89] as well as mystical and spiritual experiences that can be potent and enduring.[90] Improvements in mood, and pleasurable experiences of perception, thought and self-experience have also been reported, although strong dysphoria, anxiety and may also occur as adverse effects.[91] With the psychedelic effects of psilocybin being the most remarkable aspect of its pharmacology and the mood altering and anxiolytic properties less predictable and sometimes adverse, a therapeutic role for psilocybin in neuropsychiatry may be limited or elusive.

Although psychedelic experiences with guided psychotherapy have been suggested to be therapeutic, not all behavioral experiences are therapeutic. Psilocybin has also been used with limited success in attempts to brainwash subjects, as for example in the well-known MK-ULTRA project run by the U.S. CIA.[92]

While there is some evidence around dosing it is unclear if the optimal dose required has been definitively established. Evidence of efficacy of psilocybin microdosing is weak.

Furthermore, there has been a paucity of high-quality research into psilocybin due to Schedule I controlled substance status for the last five decades. Despite recent studies, the body of literature supporting the clinical efficacy of psilocybin remains preliminary.

This literature is also beset by significant methodological questions which need to be addressed by the next generation of studies. Blinding and the driving of expectancy is a very important challenge. Acute administration of any overtly euphorigenic agent unblinds administration and is a powerful driver of expectancy and hence placebo effects.[93] This is particularly the case in people who have had persistent or unremitting depression and anxiety, where relief, let alone euphoria can be one of the most robust drivers of expectancy and hence nonspecific treatment effects. It is worth noting that several of the trials cited above used the QIDS-SR-16 which is a self-rated (SR) scale, which is problematic when blinding is inadequate. The next generation of studies may well require innovative solutions such as psychoactive controls to mitigate the euphoria inducing effects of medication or administration under sedation to minimize unblinding and expectancy. If psilocybin does become a pharmacotherapeutic agent, careful formal pharmacovigilance and postmarketing surveillance will be crucial.

Next generation research may even bypass psilocybin and other hallucinogens altogether, with psychoplastogens currently being developed.[38] These agents share neuroplastic mechanisms with classical psychedelics, but without the hallucinogenic experiences and there is preclinical data to demonstrate robust effects on structural plasticity in the prefrontal cortex.[94] However, human trials of nonhallucinogenic psychoplastogens have not been conducted and the relationship between synaptogenesis or dendritogenesis in rodents and clinical outcomes in humans is not known.

There are three principal bridges to cross. Firstly, definitive data regarding efficacy is required arising from studies that have dealt with the major methodological problems bedeviling the field to date such as blinding and expectancy. Secondly, because most psychiatric disorders are enduring, long term data regarding both safety and efficacy is required. It is not possible to extrapolate from acute data because of tachyphylaxis associated with many recreational drugs and uncertainty about long term effects. Lastly but most importantly the pivotal issue remains safety. The small trials to date are inadequately powered to detect relatively rare risks such as psychosis which can be life changing. The opiate experience is informative in this regard because risks did not emerge in the well-controlled environment of clinical trials for pain but did so in the far less regulated clinical environment especially when it abuts into the chaotic world of recreational use. The number needed to harm (NNH) regarding risks like psychosis needs to be calibrated. Additionally other risks such as the use of one repurposed recreational drug serving as a gateway to experimentation with other recreational drugs for self-medication in the real world remains uncertain. Careful evaluation of the number needed to harm against the number needed to treat (NNT) will ultimately be needed to justify the clinical use of psilocybin. These issues need to be addressed before the field can embrace psilocybin and other psychedelics.

Conclusion

There is a paucity of research into the efficacy and safety of psilocybin. There is some evidence to suggest that it may benefit people with anxiety and depression due to cancer. Additionally, psilocybin may be a treatment option for people with treatment-resistant depression although the existing literature has significant methodological challenges that limited definitive extrapolation. Benefit seems to be obtained from doses sufficient to generate hallucinogenic experiences in participants who have been prepared for the experience with psilocybin administered in supported sessions. There is limited evidence to suggest a role for psilocybin for treating high prevalence disorders, depression and anxiety, and further research is required to identify risks and benefits as well as to identify individual patient characteristics or patient groups that may receive the greatest benefit. Further research and potential therapeutic use of psilocybin is limited by its status as a schedule 1 substance and risk of abuse and behavioral effects by recreational drug users.

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