

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/316763693>

Psilocybin-Assisted Therapy: A Review of a Novel Treatment for Psychiatric Disorders

Article in *Journal of Psychoactive Drugs* · May 2017

DOI: 10.1080/02791072.2017.1320734

CITATIONS

38

READS

5,176

3 authors, including:



Kelan LH Thomas

Touro University California

30 PUBLICATIONS 1,680 CITATIONS

[SEE PROFILE](#)



Benjamin Malcolm

Spirit Pharmacist

19 PUBLICATIONS 220 CITATIONS

[SEE PROFILE](#)

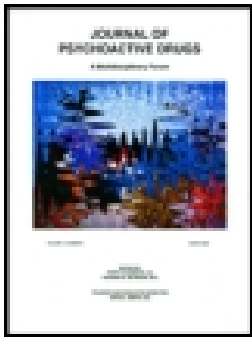
Some of the authors of this publication are also working on these related projects:



Side Effects of Drugs Annual [View project](#)



MDMA in Subjects With Moderate Hepatic Impairment and Subjects With Normal Hepatic Function [View project](#)



Psilocybin-Assisted Therapy: A Review of a Novel Treatment for Psychiatric Disorders

Kelan Thomas Pharm.D., M.S., Benjamin Malcolm Pharm.D., M.P.H. & Dan Lastra B.S.

To cite this article: Kelan Thomas Pharm.D., M.S., Benjamin Malcolm Pharm.D., M.P.H. & Dan Lastra B.S. (2017): Psilocybin-Assisted Therapy: A Review of a Novel Treatment for Psychiatric Disorders, Journal of Psychoactive Drugs

To link to this article: <http://dx.doi.org/10.1080/02791072.2017.1320734>



Published online: 08 May 2017.



Submit your article to this journal [↗](#)



View related articles [↗](#)



View Crossmark data [↗](#)

Psilocybin-Assisted Therapy: A Review of a Novel Treatment for Psychiatric Disorders

Kelan Thomas, Pharm.D., M.S. ^a, Benjamin Malcolm, Pharm.D., M.P.H.^b, and Dan Lastra, B.S.^c

^aAssistant Professor, Clinical Sciences, Touro University California, Vallejo, CA, USA; ^bAssistant Professor, Pharmacy Practice and Administration, Western University of Health Sciences, Pomona, CA, USA; ^cPharmacy Student, Touro University California, Vallejo, CA, USA

Abstract

Recent research suggests that functional connectivity changes may be involved in the pathophysiology of psychiatric disorders. Hyperconnectivity in the default mode network has been associated with psychopathology, but psychedelic serotonin agonists like psilocybin may profoundly disrupt these dysfunctional neural network circuits and provide a novel treatment for psychiatric disorders. We have reviewed the current literature to investigate the efficacy and safety of psilocybin-assisted therapy for the treatment of psychiatric disorders. There were seven clinical trials that investigated psilocybin-assisted therapy as a treatment for psychiatric disorders related to anxiety, depression, and substance use. All trials demonstrated reductions in psychiatric rating scale scores or increased response and remission rates. There were large effect sizes related to improved depression and anxiety symptoms. Psilocybin may also potentially reduce alcohol or tobacco use and increase abstinence rates in addiction, but the benefits of these two trials were less clear due to open-label study designs without statistical analysis. Psilocybin-assisted therapy efficacy and safety appear promising, but more robust clinical trials will be required to support FDA approval and identify the potential role in clinical psychiatry.

ARTICLE HISTORY

Received 9 January 2017
Revised 13 March 2017
Accepted 20 March 2017

Keywords

Anxiety; depression;
psilocybin; psychedelic;
substance use

It has been suggested that the psychedelic compound lysergic diethylamide (LSD) may have been one catalyst for ushering in the modern era of molecular psychiatry during the early 1950s since, roughly a decade after Albert Hoffman discovered LSD, other researchers first recognized the chemically similar endogenous neurotransmitter serotonin (Nichols 2004). Interest in these psychedelic compounds has been recently renewed for investigating the therapeutic potential of serotonin (5-HT) agonists, like psilocybin, and also learning more about brain activity with these compounds (Nichols 2016).

Advances in neuroimaging technology have enabled a more robust investigation of the human brain than was possible in the 1950s, when the first edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) was published and the earliest psychiatric medications received FDA approval. These advances in technology have prompted the National Institute of Mental Health (NIMH) to propose the Research Domain Criteria (RDoC) project research initiative in 2009, which provided a framework for new ways of studying mental disorders that may eventually inform a more objective diagnostic paradigm than the current nosology of symptom clusters from the DSM (Cuthbert 2015). This

RDoC framework consists of a matrix specifying functional constructs characterized in aggregate by the genes, molecules, and circuits used to measure human behavior (Cuthbert 2015). In one line of research inquiry consistent with the RDoC framework, Menon (2011) has formulated a unifying triple network model of psychopathology and suggested that depression may be characterized by enhanced functional connectivity with other nodes of the default mode network (DMN) for pregenual and subgenual-cingulate cortex (SCC), along with adjoining ventromedial prefrontal cortex (vmPFC). The DMN connectivity in one neuroimaging study was defined by posterior-cingulate cortex (PCC) connectivity, which was stronger for SCC in major depressive disorder (MDD) patients than healthy controls ($p < 0.05$) (Berman et al. 2010). The subjective scores on the Rumination Response Styles (RRS) inventory were also positively correlated with SCC-PCC connectivity ($r = 0.68, p < 0.001$) and researchers concluded that DMN hyperconnectivity could potentially explain the excessive ruminating thoughts of depressed patients (Berman et al. 2010). Interestingly, SCC functional connectivity in the DMN has also been positively correlated with duration of the current depressive episode ($r = 0.49, p = 0.014$) (Greicius et al. 2007).

This emerging evidence may necessitate a paradigm shift in how we understand psychiatric disorders and may offer new explanations for why such disparate treatment modalities like electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), ketamine infusion, and psilocybin-assisted therapy all rapidly reduce depression symptoms. More recently, there have been a series of neuroimaging studies specifically investigating the effects of psilocybin on functional connectivity networks in the brain (Carhart-Harris et al. 2012; Muthukumaraswamy et al. 2013; Roseman et al. 2014). A recent review evaluating these psychedelic neuroimaging studies speculated on psilocybin's possible mechanism of action for treating psychiatric disorders: "following psychedelic-induced disintegration within local networks, as well as increased global interconnectivity, connections responsible for psychiatric-disorder-associated hub failures are disrupted and broken by the emergence of strong, topologically long-range functional connections. Then, as the effect of the drug wears off, networks can reconnect in 'healthy' ways, in the absence of the pathological driving forces(s) that originally led to a hub failure and disease" (Nichols, Johnson, and Nichols 2017). The purpose of this article is to review the pharmacokinetics, pharmacodynamics, and clinical evidence for psilocybin-assisted therapy as a novel treatment approach for psychiatric disorders related to anxiety, depression, and substance use.

Methods

We reviewed the available literature in order to investigate the potential role of psilocybin-assisted therapy for treating psychiatric disorders. A PubMed search was performed for "Clinical Trial" articles on the topic of "psilocybin and psychiatry" published through December 31, 2016. We also performed a PubMed search on the topics of "psilocybin," "pharmacokinetics," and "pharmacodynamics" to provide background drug information about this novel therapeutic agent with emerging clinical evidence.

Results

Pharmacokinetics

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is a substituted indolealkylamine from the tryptamine group of compounds (Passie et al. 2002). Psilocybin was shown to rapidly dephosphorylate to an active metabolite, psilocin, by alkaline phosphatase and nonspecific esterase in the intestinal mucosa (Tylš, Páleníček, and Horáček 2014). There may be a first-pass effect with psilocybin based on the very low psilocin levels at the time to peak plasma concentration (t_{max}) and relatively higher levels

of the inactive metabolite 4-hydroxy-indole-3-acetic acid (4HIAA) (Hasler et al. 1997). It remains unknown if any specific cytochrome P450 enzymes catalyze the formation of psilocybin metabolites, since human studies of pharmacokinetic parameters are limited (Yu 2008). Psilocin was also found to be glucuronidated by UDP-glucuronosyltransferases (UGTs) into psilocin glucuronide, with the greatest activity from UGT1A10 in the small intestine and then UGT1A9 in the liver (Manevski et al. 2010). Psilocin was shown to be renally excreted, partially in the form of psilocin glucuronide, and the lower limit of quantitation for psilocin in urine samples (10 $\mu\text{g/L}$) was usually reached 24 hours after ingestion (Hasler et al. 2002).

Psilocybin administered intravenously (IV) demonstrated a psilocin mean terminal elimination half-life ($t_{1/2\beta}$) of 74 minutes, but psilocin's half-life was 163 minutes when psilocybin was given by mouth (PO), which suggests that there may be a dose-dependent effect on metabolism (Hasler et al. 1997). Another study measuring PO psilocybin pharmacokinetic parameters demonstrated a similar psilocin half-life ($t_{1/2}$) of 135 minutes, elimination constant (k_e) of 0.307/h, and absorption constant (k_a) of 1.307/h (Lindenblatt et al. 1998). Psilocin's bioavailability is estimated to be 52.7% after PO psilocybin administration (10–20 mg), with plasma levels detectable 20 to 90 minutes after ingestion (t_{max} = 85–180 min) and perceptible psychological effects at psilocin plasma levels ranging from 4 to 6 ng/ml (Hasler et al. 1997).

Pharmacodynamics

Most classic psychedelics, including psilocybin, are non-selective serotonin agonists with psychoactive effects related to agonism of the 5-hydroxytryptamine 2A (5-HT_{2A}) receptor subtype (Lebedev et al. 2015; Nichols 2016). Psilocin binds with the highest affinity to 5-HT_{2A} (K_i = 6 nM) and to a lesser extent 5-HT_{1A} (K_i = 190 nM), with relatively lower affinity for other serotonin receptors (McKenna et al. 1990). Agonism of the 5-HT_{2A} receptor stimulates phospholipase C (PLC) via G_{q/11}, which leads to downstream activation of protein kinase C (PKC) and an increased release of Ca²⁺ from intracellular stores (Baumeister et al. 2014). Another independent 5-HT_{2A} receptor activation signaling pathway stimulates phospholipase A₂ (PLA₂), which can hydrolyze phospholipids and produce free arachidonic acid (Nichols 2004).

Psilocybin's psychological effects have been attributed to the 5-HT_{2A} receptor, since the 5-HT_{2A} antagonist ketanserin has reversed psilocybin-induced effects, such as enhanced positive mood and attenuated recognition of negative facial expression (Kometer et al. 2012).

Ketanserin also reduced psilocybin-induced subjective psychological effects like oceanic boundlessness (Δ ~700 points) and visionary restructuring (Δ ~500 points) as measured by the 5-Dimensions Altered States of Consciousness (5D-ASC) 94-item questionnaire self-rating scale ($p < 0.0002$), along with decreasing psilocybin-induced mean error rates in the conflict condition of the Stroop test (~4 vs. ~2 errors, $p < 0.0001$) (Quednow et al. 2012). Pretreatment with ketanserin also prevented the psilocybin-induced reductions in the acoustic startle response measured by prepulse inhibition (PPI) at short lead intervals ($p < 0.008$) (Quednow et al. 2012). These studies provide compelling evidence that psilocybin's psychological effects are mediated primarily by agonism at the 5-HT_{2A} receptor subtype.

This 5-HT_{2A} receptor agonism may be especially significant in the cerebral cortex, since *in vitro* light microscopic autoradiography has demonstrated exceptionally high concentrations of 5-HT_{2A} receptors localized over layer III and V pyramidal neurons of several cortical areas in postmortem brain tissue (Pazos, Probst, and Palacios 1987). The activation of the 5-HT_{2A} receptors in the reticular nucleus may inhibit thalamic filtering of information via GABAergic projections, potentially allowing cortical areas to receive more sensory information passing through (Baumeister et al. 2014). Dynamic causal modeling has also demonstrated that deep-layer pyramidal cell excitation could provide a net effect of feedback inhibition, which would be consistent with the decreased brain activity and oscillatory power shown on magnetic encephalography (MEG) after psilocybin administration (Muthukumaraswamy et al. 2013).

In addition to high 5-HT_{2A} receptor expression in the cortex, there are also 5-HT_{2A} receptors in the periphery, where agonism has been associated with contraction of vascular smooth muscle and platelet aggregation (Nagatomo et al. 2004). Due to the potential risk of cardiovascular adverse reactions, psilocybin clinical trials have frequently monitored cardiac vital signs for safety. In one landmark clinical trial evaluating psilocybin-occasioned mystical-type experiences, psilocybin demonstrated dose- and time-related effects on cardiac vital signs with a higher mean systolic blood pressure (SBP Δ 20.5 mm Hg), diastolic BP (DBP Δ 11.3 mm Hg), and heart rate (HR Δ 8.2 bpm) than placebo ($p < 0.05$) in the highest dose condition (30 mg/70 kg), which were transient and normalized six hours post-dose (Griffiths et al. 2006).

Clinical trials for cancer-related anxiety and depressive disorders

Grob et al. (2011) conducted the first double-blind, placebo-controlled, crossover study of 12 participants

with advanced-stage cancer and reactive anxiety, which was defined by a DSM-IV diagnosis of acute stress disorder, generalized anxiety disorder (GAD), anxiety disorder due to cancer, or adjustment disorder with anxiety. Participants met with study staff for a preparatory session to discuss expectations and goals of the two experimental sessions. During each of the two six-hour experimental sessions, separated by several weeks, participants were given either a dose of psilocybin (0.2 mg/kg) or niacin placebo (250 mg), along with psychological support. During the second experimental session, each participant was given the opposite treatment they were randomized to in the first session and followed for six months. The main outcomes were cardiac safety (SBP, DBP, HR) and subjective experience (5D-ASC) during the sessions, followed by Beck Depression Inventory (BDI), Profile of Mood States (POMS), and State-Trait Anxiety Inventory (STAI) efficacy measures at monthly intervals for six months after the second experimental session. Participants wore a Holter cardiac monitor for 24 hours, which started at admission and included the entire experimental dose session (Grob et al. 2011).

Mean BDI after psilocybin was lower than baseline after six months (~ Δ 9 points, $p = 0.03$), while mean STAI trait anxiety score was lower than baseline after one month (~ Δ 7, $p = 0.001$) and three months (~ Δ 6, $p = 0.03$) (Grob et al. 2011). Mean POMS was not significantly different than mean baseline score at any time point during the six months. Psilocybin increased cardiac vital signs during the session between 1–5 hours after psilocybin administration that peaked at two hours, when HR and SBP were greater than placebo, while DBP was not: mean HR 81.5 vs. 70.4 bpm ($p < 0.007$); mean SBP 138.9 vs. 117.0 mm Hg ($p < 0.01$); mean DBP 75.9 vs. 69.6 mm Hg (Grob et al. 2011).

Ross et al. (2016) also conducted a double-blind, placebo-controlled, crossover study of 29 participants with cancer-related anxiety and depression. The majority met DSM-IV criteria for an adjustment disorder with anxiety ($n = 26$), while the rest ($n = 3$) met criteria for GAD. Participants met with study staff for three two-hour preparatory sessions to discuss expectations and goals of the experimental sessions. During each of the two six-hour experimental sessions, separated by seven weeks, participants were either given a dose of psilocybin (0.3 mg/kg) or niacin placebo (250 mg), along with psychological support. During the second experimental session, each participant was given the opposite treatment they were randomized to in the first session and followed for another 6.5 months. The primary outcomes of cancer-related anxiety and depression improvements and response/remission were measured by self-reported

STAI for anxiety, along with Hospital Anxiety Depression Scale (HADS) and BDI for depression, using the following rating subscales: STAI-State (STAI-S), STAI-Trait (STAI-T), HADS Anxiety (HAD-A), HADS Depression (HAD-D), HADS Total (HAD-T), and BDI. These primary outcome variables were measured pre-crossover at baseline, one day pre-dose 1, one day post-dose 1, two weeks post-dose 1, six weeks post-dose 1, and seven weeks post-dose 1 (Ross et al. 2016).

After seven weeks post-dose 1, participants first receiving psilocybin had lower mean scores on all six rating subscales than the participants receiving niacin first ($p < 0.05$) (Ross et al. 2016). The difference in mean HAD-T scores between groups at seven weeks post-dose was $\sim\Delta 7$, which demonstrated the largest effect size of the primary outcomes, represented by Cohen's $d = 1.36$ ($p \leq 0.001$). The other seven weeks post-dose 1 estimated differences in mean scores between groups, with corresponding Cohen's d values and p -values as follows: STAI-T $\sim\Delta 10$, $d = 1.29$, $p \leq 0.001$; STAI-S $\sim\Delta 12$, $d = 1.18$, $p \leq 0.01$; HAD-A $\sim\Delta 3$, $d = 1.07$, $p \leq 0.01$; HAD-D $\sim\Delta 3$, $d = 0.98$, $p \leq 0.01$; HAD-T $\sim\Delta 7$, $d = 1.36$, $p \leq 0.001$; BDI $\sim\Delta 6$, $d = 0.82$, $p < 0.05$. The depression response was defined by a $\geq 50\%$ reduction in score, while remission was defined by a $\geq 50\%$ reduction plus HAD-D ≤ 7 or BDI ≤ 12 . The following depression response or remission rates at seven weeks post-dose 1 were higher for participants first receiving psilocybin than the niacin placebo: response rates by HAD-A (58% vs. 14%, $p \leq 0.01$), HAD-T ($\sim 70\%$ vs. $\sim 20\%$, $p \leq 0.01$), and BDI (83% vs. 14%, $p \leq 0.01$), along with remission rates by BDI ($\sim 80\%$ vs. $\sim 15\%$, $p \leq 0.01$). The subjective effects of the psilocybin sessions, measured by the Mystical Experience Questionnaire (MEQ) total score, were also positively correlated with the magnitude of score change for the following primary outcomes: STAI-T, $r = 0.40$, $p = 0.04$; STAI-S, $r = 0.42$, $p = 0.03$; HAD-T, $r = 0.49$, $p = 0.009$; HAD-A, $r = 0.46$, $p = 0.01$ (Ross et al. 2016).

The most common adverse events related to psilocybin were elevations in BP and HR (76%), headaches (28%), transient anxiety (17%), nausea (14%), and transient psychotic-like symptoms (7%) (Ross et al. 2016). The mean SBP peaked at ~ 142 mm Hg, 180 minutes after psilocybin administration, but was higher than the niacin placebo at time points between 60 to 300 minutes post-dose ($p \leq 0.01$). The mean DBP peaked at ~ 82 mm Hg, 180 minutes after psilocybin administration, but was higher than the niacin placebo at time points between 60 to 240 minutes post-dose ($p < 0.05$). The mean heart rate was relatively consistent at ~ 70 bpm after psilocybin administration, but was higher than the niacin placebo

at time points between 90 to 120 minutes post-dose ($p < 0.05$), primarily due to heart rate reductions from baseline with the niacin placebo (Ross et al. 2016).

Griffiths et al. (2016) conducted a randomized, double-blind, crossover study of 51 cancer participants with life-threatening diagnoses and symptoms of depression and/or anxiety. The participants with a life-threatening cancer diagnosis also met DSM-IV criteria for chronic adjustment disorder with anxiety ($n = 11$), chronic adjustment disorder with mixed anxiety and depressed mood ($n = 11$), GAD ($n = 5$), dysthymic disorder ($n = 5$), MDD ($n = 14$), comorbid GAD with MDD ($n = 5$), or GAD with dysthymic disorder ($n = 1$). Participants met with study staff for two or more preparatory sessions to discuss expectations and goals of the two experimental sessions. During each of the two approximately six-hour experimental sessions, separated by approximately five weeks, participants were given either high-dose psilocybin (22 or 30 mg/70 kg) or low-dose psilocybin (1 or 3 mg/70 kg), along with psychological support. During the second experimental session, each participant was given the opposite treatment they were randomized to in the first session. The primary outcomes of depression and anxiety response and remission were measured by the GRID-Hamilton Depression Rating Scale (GRID-HAMD-17) and the structured interview guide for the Hamilton Anxiety Rating Scale (HAM-A assessed with SIGH-A). The depression or anxiety response was defined by a $\geq 50\%$ reduction in score, while remission was defined by a $\geq 50\%$ reduction plus GRID-HAMD-17 or HAM-A ≤ 7 , respectively. These primary outcome variables were measured at baseline, five weeks post-session 1, five weeks post-session 2, and six months after baseline. Secondary outcome rating scales measured included the BDI, HAD-T, HAD-D, HAD-A, HAM-A, and STAI-T, among others (Griffiths et al. 2016).

The GRID-HAMD-17 response rates (92% vs. 32%, $p < 0.001$), HAM-A response rates (76% vs. 24%, $p < 0.001$), GRID-HAMD-17 remission rates (60% vs. 16%, $p < 0.01$), and HAM-A remission rates (52% vs. 12%, $p < 0.01$) were all higher for participants receiving high-dose psilocybin first than low-dose psilocybin first at five weeks post-session 1 (Griffiths et al. 2016). After a six-month follow-up, the response and remission rates were sustained, as demonstrated by a nonsignificant difference between post-session 1 vs. six months in the high-dose first group or between post-session 2 vs. six months in the low-dose first group on these outcomes. The rating scales reductions in mean scores for participants receiving the high-dose first, were greater than participants receiving low-dose first, were as follows: GRID-HAMD-17 $\Delta 8.2$ ($p < 0.001$), BDI $\Delta 5.9$

($p < 0.01$), HAD-D $\Delta 2.1$ ($p < 0.05$), HAM-A $\Delta 8.2$ ($p < 0.001$), and STAI-T $\Delta 5.8$ ($p < 0.05$). The subjective effects of the psilocybin sessions, measured by MEQ total score, were also correlated with a reduction in scores on the HAM-A ($r = -0.59$, $p < 0.0001$) and HAD-D ($r = -0.36$, $p < 0.01$) rating scales (Griffiths et al. 2016).

Adverse events appeared to be more frequent in the high-dose vs. low-dose psilocybin sessions, with more participants experiencing episodes of transient elevated SBP (> 160 mm Hg: 34% vs. 17%), elevated DBP (> 100 mm Hg: 13% vs. 2%), nausea/vomiting (15% vs. 0%), physical discomfort (21% vs. 8%), anxiety (26% vs. 15%), psychological discomfort (32% vs. 12%), and paranoid ideation (2% vs. 0%), but these transient episodic events were not statistically tested for any differences (Griffiths et al. 2016).

Clinical trial for treatment-resistant major depressive disorder

Carhart-Harris et al. (2016) conducted an open-label pilot study of 12 participants with moderate to severe MDD who already failed adequate trials (> 6 weeks) with at least two antidepressants. An initial four-hour preparatory psychotherapy session was completed prior to the first dose of psilocybin. During the first treatment session, a low dose of psilocybin (10 mg) was administered along with psychological support. One week after the low-dose safety session, each participant completed a high-dose (25 mg) session and was followed for assessments at several time points: one week, two weeks, three weeks, five weeks, and three months. The primary outcome was the difference in the Quick Inventory of Depressive Symptoms (QIDS) scores from baseline to one week after the high-dose session, but other rating scales measured included the BDI, HAM-D, STAI-T, among others (Carhart-Harris et al. 2016).

The mean baseline QIDS was 19.2, while the mean difference after one week was -11.8 (95% CI: -9.15 to -14.35 ; Hedges' $g = 3.1$) and after three months was -9.2 (95% CI: -5.69 to -12.71 ; Hedges' $g = 2$) (Carhart-Harris et al. 2016). The mean differences on other rating scales after one week were as follows: BDI -25.0 (95% CI: -20.1 to -29.9 ; Hedges' $g = 3.2$), HAM-D -14.0 (95% CI: -9.6 to -18.4 ; Hedges' $g = 2.4$), STAI-T -29.5 (95% CI: -22.03 to -36.97 ; Hedges' $g = 2.7$). Adverse events reported during the psilocybin sessions included transient anxiety (100%), confusion or thought disorder (75%), nausea (33%), headache (33%), and paranoia (8%) (Carhart-Harris et al. 2016).

Clinical trial for obsessive-compulsive disorder

Moreno et al. (2006) conducted an open-label, dose-escalation study with nine participants diagnosed with obsessive-compulsive disorder (OCD) who failed an adequate trial (> 12 weeks) with at least one serotonin reuptake inhibitor. Participants received up to four doses of psilocybin with at least a week between sessions. Doses were administered in an escalating fashion (0.1 mg/kg, 0.2 mg/kg, 0.3 mg/kg) with the exception of a very-low-dose session of 0.025 mg/kg, which was given in random sequence any time after the first 0.1 mg/kg dose. The Yale Brown Obsessive-Compulsive Scale (YBOCS) and a visual analog scale (VAS) for overall OCD symptom severity were administered prior to psilocybin ingestion and at 4, 8, and 24 hours after ingestion. A Hallucinogen Rating Scale (HRS) was also administered once, eight hours after ingestion (Moreno et al. 2006).

A repeated measures ANOVA was used to analyze efficacy with YBOCS values, which demonstrated a significant main effect of time ($p = 0.046$), although there was no effect of dose or interaction of dose and time (Moreno et al. 2006). The combined baseline mean YBOCS scores, when stratified by dose groups, ranged from 18.3 to 24.1, were reduced 24 hours after psilocybin administration, and then ranged from 10.7 to 11.3 ($p = 0.028$). Durability of response was not studied formally, but two participants reported symptomatic improvement lasting most of the week and one participant achieved long-term remission measured after six months. The only adverse reaction reported was mild and transient hypertension in one participant, with BP peaking at 142/105 mm Hg four hours after administration (Moreno et al. 2006).

Clinical trial for alcohol dependence

Bogenschutz et al. (2015) conducted an open-label proof of concept study in 10 participants who met DSM-IV criteria for alcohol dependence, drank heavily (females ≥ 4 /day, males ≥ 5 /day) at least two of the past 30 days, and were concerned about their drinking. Weekly psychotherapy was provided over 12 weeks, with four sessions prior to the first psilocybin session, four between the psilocybin sessions, and four after the second psilocybin session. Psychotherapy sessions consisted of three preparatory sessions, seven motivational enhancement therapy sessions, and two debriefing sessions. Psilocybin was administered at a dose of 0.3 mg/kg during the first session and 0.4 mg/kg during the second session, with the exception of one participant who received 0.3 mg/kg for both sessions. The primary

outcome to determine response was the difference in percent heavy drinking days, assessed by the Time-Line Follow-Back procedure, in participants at baseline (during 12 weeks prior to enrollment) and during weeks 5 to 12 (one to eight weeks after first psilocybin session) of the study. Participants were also followed up at 36 weeks and completed an Addiction Research Inventory (ARCI) after each psilocybin session. Acute effects of psilocybin were captured using self-report scales by participants seven hours after ingestion, including intensity subscales of the HRS, 5D-ASC questionnaire, and MEQ (Bogenschutz et al. 2015).

The mean percent heavy drinking days was ~35% at baseline, which decreased between one to eight weeks after the first psilocybin session to ~9% (mean difference = -26.0, 95% CI -8.7 to -43.2). Reductions in heavy drinking were not present during the four weeks prior to the first psilocybin session, but the reductions one to eight weeks after the psilocybin session persisted for 32 weeks. Intensity of subjective psilocybin experiences varied greatly and was negatively correlated with percent of heavy drinking days, which demonstrated that a greater intensity of subjective effects on HRS intensity subscale ($r = -0.76$, $p = 0.017$), 5D-ASC ($r = -0.89$, $p = 0.001$), and MEQ ($r = -0.85$, $p = 0.004$) was correlated with less heavy drinking days. Psilocybin also produced transient increases in BP between 30 to 180 minutes after ingestion and peaked at ~150/90. Other treatment-related adverse events included mild headache (50%), emesis (10%), diarrhea (10%), and insomnia (10%) (Bogenschutz et al. 2015).

Clinical trial for tobacco addiction

Johnson et al. (2014) conducted an open-label pilot study to assess the feasibility of a psilocybin-based intervention for treating tobacco addiction in 15 participants who completed the trial. All participants smoked at least 10 cigarettes per day, had multiple past quit attempts and a present desire to quit smoking. A 15-week smoking cessation protocol was followed with psilocybin sessions at weeks 5, 7, and 13 along with weekly cognitive behavioral therapy (CBT) sessions for smoking cessation during the weeks psilocybin was not administered. Each participant set a target quit date coinciding with the first psilocybin session during week 5 of the study. Participants received 20 mg/70 kg (0.29 mg/kg) at week 5 and optionally increased to 30 mg/70 kg (0.43 mg/kg) during weeks 7 and 13. Participants were instructed to abstain from other medications for smoking cessation during the study period, although one participant reported use of nicotine lozenges. The primary outcome of remission

was self-reported, biologically supported, seven-day point prevalence abstinence at six months. Acute effects of psilocybin were measured using the States of Consciousness Questionnaire (SOCQ) and post-session headache interview (Johnson et al. 2014).

There were 12 (80%) who were abstinent after six months and 10 (67%) who were abstinent after 12 months (Johnson et al. 2014; Johnson, Garcia-Romeu, and Griffiths 2016). Three of the 12 who were abstinent reported self-corrected relapses in the period between the psilocybin session and the six-month follow up. Psilocybin appeared to increase peak BP and HR over baseline readings 1.5 to 2.5 hours after ingestion: mean SBP 153 vs. 125 mm Hg; DBP 87 vs. 71 mm Hg; and HR 87 vs. 68 bpm; but these differences were not statistically tested. The SOCQ revealed that 40% of participants experienced strong or extreme ratings of fear, fear of insanity, or feeling trapped at some time during the moderate or high-dose psilocybin sessions, but these were managed with interpersonal support and had resolved by the end of the session (Johnson et al. 2014).

Discussion

New clinical evidence for psilocybin-assisted therapy in psychiatry has emerged during the past decade, represented by seven studies with a combined total of 135 participants (Table 1). The large effect sizes (Hedges' $g > 2$) demonstrated in some of these small studies warrant more robust clinical trials to ascertain psilocybin's efficacy for specific psychiatric indications. This novel treatment approach with limited psilocybin therapy sessions would be remarkably different from the current treatment paradigm of daily medication. However, there is some precedent for using alternative treatment modalities with limited sessions when depressed patients fail antidepressants, such as ketamine infusion, ECT, or TMS. One important distinction from these other session-based treatments would be that the benefits of psilocybin-assisted therapy may only require a few dosing sessions and the effects appear to persist longer than other treatment options.

Another distinction is the use of psychotherapy before, during, and after the psilocybin sessions. While these studies demonstrated that psilocybin-assisted psychotherapy improved symptoms more than psychotherapy alone, it is unclear what clinical benefit (if any) would be derived from psilocybin alone, since there were no experimental conditions omitting supportive psychotherapy. A psilocybin-alone experimental condition may have been deemed unethical, since Griffiths et al. (2006) suggested that previous research had already documented that more preparation and interpersonal

Table 1. Summary of psilocybin-assisted therapy clinical trial designs and outcomes.

Publication, Study Design & Population	Experimental Session Exposures & Primary Outcome Measures	Adverse Drug Reactions	Efficacy Primary Outcomes
Moreno et al. 2006 Open-label dose-escalation trial for OCD n = 9	4 sessions \geq 1 week apart: -psilocybin 0.025 mg/kg -psilocybin 0.1 mg/kg -psilocybin 0.2 mg/kg -psilocybin 0.3 mg/kg Outcomes Yale-Brown Obsessive Compulsive Scale (YBOCS) for OCD	Frequency: transient hypertension (11%)	YBOCS mean ~10 points lower than baseline ($p = 0.028$) at 24 hours post-dose
Grob et al. 2011 Double-blind, placebo-controlled crossover for cancer-related reactive anxiety n = 12	2 sessions several weeks apart: -psilocybin 0.2 mg/kg -niacin 250 mg (placebo) Outcomes Beck Depression Inventory (BDI) for depression; State Trait Anxiety Index Trait (STAI-T) and State (STAI-S) for anxiety	Cardiovascular peak effects (2 h post-dose): SBP mean 138.9 vs. 117.0 mm Hg ($p < 0.01$); HR mean 81.5 bpm vs. 70.4 bpm ($p < 0.007$)	BDI mean ~9 points lower than baseline ($p = 0.03$) at 6 months post-dose STAI-T mean ~7 points lower than baseline after ($p = 0.001$) at 1 month post-dose STAI-T mean ~6 points lower than baseline ($p = 0.03$) at 3 months post-dose QIDS mean <i>difference</i> from baseline -11.8 (95% CI: -9.15 to -14.35, g = 3.1) at 1 week post-high dose
Carhart-Harris et al. 2016 Open-label for treatment-resistant MDD n = 12	2 sessions 1 week apart: -psilocybin 10 mg (low) -psilocybin 25 mg (high) Outcome Quick Inventory of Depressive Symptomatology (QIDS) for depression	Frequency: transient anxiety (100%), confusion or thought disorder (75%), nausea (33%), headache (33%), paranoia (8%)	BDI mean ~6-points lower than placebo ($p < 0.05$, d = 0.82); BDI higher <i>response rate</i> 83% vs. 14% ($p \leq 0.01$) and <i>remission rate</i> ~80% vs. ~15% , $p \leq 0.01$ at 7 weeks post-dose HAD-T mean ~7-points lower than placebo ($p \leq 0.001$, d = 1.36); HAD-T higher <i>response rate</i> ~70% vs. ~20% ($p \leq 0.01$) at 7 weeks post-dose HAD-A mean ~3-points lower than placebo ($p \leq 0.01$, d = 1.07); HAD-A higher <i>response rate</i> 58% vs. 14% ($p \leq 0.01$) at 7 weeks post-dose
Ross et al. 2016 Double-blind, placebo-controlled crossover for cancer-related anxiety and depression n = 29	2 sessions 7 weeks apart: -psilocybin 0.3 mg/kg -niacin 250 mg (placebo) Outcomes Hospital Anxiety Depression Scale Total (HAD-T) and Anxiety (HAD-A) or Depression (HAD-D) subscales for anxiety and depression, respectively; Beck Depression Inventory (BDI) for depression; State Trait Anxiety Index Trait (STAI-T) and State (STAI-S) for anxiety; <i>Response</i> : $\geq 50\%$ reduction in score from baseline; <i>Remission</i> : $\geq 50\%$ reduction in score from baseline plus BDI ≤ 12	Frequency: transient elevations in BP and HR (76%), headaches (28%), anxiety (17%), nausea (14%), psychotic-like symptoms (7%) Cardiovascular effects: SBP mean ~ 142 mm Hg peaked at 180 min, but was higher than placebo from 60–300 min post-dose ($p \leq 0.01$) Mean DBP ~ 82 mm Hg peaked at 180 min, but was higher than placebo from 60–240 min post-dose ($p < 0.05$) Mean HR ~ 70 mm Hg consistent, but was higher than placebo from 90–120 min post-dose ($p < 0.05$)	BDI mean ~6-points lower than placebo ($p < 0.05$, d = 0.82); BDI higher <i>response rate</i> 83% vs. 14% ($p \leq 0.01$) and <i>remission rate</i> ~80% vs. ~15% , $p \leq 0.01$ at 7 weeks post-dose HAD-T mean ~7-points lower than placebo ($p \leq 0.001$, d = 1.36); HAD-T higher <i>response rate</i> ~70% vs. ~20% ($p \leq 0.01$) at 7 weeks post-dose HAD-A mean ~3-points lower than placebo ($p \leq 0.01$, d = 1.07); HAD-A higher <i>response rate</i> 58% vs. 14% ($p \leq 0.01$) at 7 weeks post-dose
Griffiths et al. 2016 Double-blind, crossover for cancer-related anxiety and depression n = 51	2 sessions ~ 5 weeks apart: -psilocybin 1 or 3 mg/70 kg (low dose) -psilocybin 22 or 30 mg/70 kg (high dose) Outcomes GRID-Hamilton Depression Rating Scale 17-item (GRID-HAMD-17); Hamilton Anxiety Rating Scale (HAM-A); <i>Response</i> : $\geq 50\%$ reduction in score from baseline; <i>Remission</i> : $\geq 50\%$ reduction in score from baseline plus GRID-HAMD-17 ≤ 7 or HAM-A ≤ 7	Frequency (high vs. low dose): transient elevated SBP > 160 mm Hg (34% vs. 17%), elevated DBP > 100 mm Hg (13% vs. 2%), nausea/vomiting (15% vs. 0%), physical discomfort (21% vs. 8%), psychological discomfort (32% vs. 12%), anxiety (26% vs. 15%), paranoid ideation (2% vs. 0%) No statistical testing	GRID-HAMD-17 mean ~8-points lower for high dose ($p \leq 0.001$); GRID-HAMD-17 <i>response rates</i> higher for high dose 92% vs. 32% ($p < 0.001$) GRID-HAMD-17 higher <i>remission rates</i> 60% vs. 16% ($p < 0.001$) at 5 weeks post-session 1 dose HAM-A mean ~8-points lower for high dose ($p \leq 0.001$); HAM-A higher <i>response rates</i> 76% vs. 24% ($p < 0.001$) HAM-A higher <i>remission rates</i> 52% vs. 12% ($p < 0.001$) at 5 weeks post-session 1 dose
Johnson et al. 2014 Johnson, Garcia-Romeu, and Griffiths 2016 Open-label for tobacco addiction n = 15	3 sessions—first on quit date, second 2 weeks later and third 6 weeks later: -psilocybin 20 mg/70 kg -optional increase to 30 mg/70 kg for second and third sessions Outcome <i>Abstinence</i> self-reported and biologically supported (urine cotinine screen) 7-day point prevalence rates	Frequency of strong or extreme fear was 40% Mean peak SBP 153 vs. 125 mm Hg; Mean peak DBP 87 vs. 71 mm Hg Mean peak HR 87 vs. 68 bpm No statistical testing	<i>Abstinence rates</i> were 80% after 6 months <i>Abstinence rates</i> were 67% after 12 months *No statistical testing
Bogenschutz et al. 2015 Open-label for alcohol dependence n = 10	2 sessions 4 weeks apart -psilocybin 0.3 mg/kg first -psilocybin 0.4 mg/kg second Outcome <i>Percent of heavy drinking days</i> 1–8 weeks after first dose session	Frequency: mild headache (50%), emesis (10%), diarrhea (10%), insomnia (10%) after any session	Mean <i>percent of heavy drinking days</i> decreased from $\sim 35\%$ at baseline to $\sim 9\%$ (-26.0% , 95% CI -8.7 to -43.2) between 1 to 8 weeks after the first dose, which persisted for 32 weeks

support decreased psychological adverse effects compared to the earliest psilocybin experiments.

Preliminary evidence also suggests that the subjective experience during the psilocybin-assisted therapy session may be important, given the positive correlation between mystical-type experiences and improved clinical outcomes (Bogenschutz et al. 2015; Griffiths et al. 2016; Ross et al. 2016). However, further research is needed to determine how subjective effects and clinical responses are related to psilocybin, psychotherapy, or the optimal synergistic combination of both.

Psilocybin-assisted therapy for depression symptoms seems to have the strongest clinical evidence thus far, with four studies demonstrating clinically significant reductions on rating scale scores and often with subsequently higher response or remission rates (Carhart-Harris et al. 2016; Griffiths et al. 2016; Grob et al. 2011; Ross et al. 2016). In these studies, reductions on the BDI, HAD-D, HAM-D, and QIDS have ranged from ~3–25 points, while response/remission rates (defined by the BDI, HAD-T, and HAM-D-17 scores) have been ~3–6-fold higher after psilocybin sessions (Carhart-Harris et al. 2016; Griffiths et al. 2016; Grob et al. 2011; Ross et al. 2016).

Psilocybin also has compelling evidence for anxiety symptoms, with four studies demonstrating significant reductions on rating scale scores and often accompanied by higher response or remission rates (Griffiths et al. 2016; Grob et al. 2011; Moreno et al. 2006; Ross et al. 2016). In these studies, reductions on the HAD-A, HAM-A, Y-BOCS, and STAI-T have ranged from ~6–30 points, while response/remission rates (defined by the HAD-A and HAM-A scores) have been ~3–4-fold higher after psilocybin sessions (Griffiths et al. 2016; Grob et al. 2011; Moreno et al. 2006; Ross et al. 2016).

The potential to treat substance use disorders has relatively weaker clinical evidence, but promising results from open-label proof-of-concept trials have prompted researchers to launch larger randomized controlled trials recruiting for target enrollments of 180 participants with alcohol use disorder (NCT02061293) and 50 participants with tobacco use disorder (NCT01943994) (Bogenschutz et al. 2015; Johnson et al. 2014; Johnson, Garcia-Romeu, and Griffiths 2016).

The safety profile for psilocybin also appears favorable, especially given the short-term exposure required for only a few sessions. The most commonly reported adverse drug reactions were transient hypertension (in some cases BP > 160/100) and psychological reactions (anxiety or fear) that appeared to resolve by the end of the experimental sessions.

Despite the large effect sizes and favorable safety profile demonstrated in these small clinical trials, it is

important to recognize that there was substantial heterogeneity in the populations enrolled, due to different DSM-IV diagnoses and comorbidities (cancer), along with different study designs and timelines for measuring endpoints. If psilocybin-assisted therapy will eventually become a therapeutic option in clinical psychiatry, future trials must employ consistent methodology to expand and replicate this emerging evidence base.

Conclusions

The psychedelic 5-HT_{2A} agonist, psilocybin, is beginning to demonstrate potential for treating psychiatric disorders related to anxiety, depression, and substance use. Psilocybin-assisted therapy is a new investigational psychiatric treatment paradigm characterized by only a few six-hour medication therapy sessions with psychological support. These psilocybin sessions, supported by several weeks of integrative psychotherapy sessions, may significantly improve symptom scores and help patients achieve response or remission within weeks, which could persist for many months after taking psilocybin.

Additional studies are required to determine if psilocybin will be deemed safe and effective enough to gain FDA approval. While psilocybin's clinical utility still remains uncertain, it should be investigated further to determine if this novel treatment paradigm has the potential to dramatically improve outcomes in patients with psychiatric disorders.

ORCID

Kelan Thomas  <http://orcid.org/0000-0003-2818-270X>

References

- Baumeister, D., G. Barnes, G. Giaroli, and D. Tracy. 2014. Classical hallucinogens as antidepressants? A review of pharmacodynamics and putative clinical roles. *Therapeutic Advances in Psychopharmacology* 4 (4):156–69. doi:10.1177/2045125314527985.
- Berman, M. G., S. Peltier, D. E. Nee, E. Kross, P. J. Deldin, and J. Jonides. 2010. Depression, rumination and the default network. *Social Cognitive and Affective Neuroscience* 6 (5):548–55.
- Bogenschutz, M. P., A. A. Forcehimes, J. A. Pommy, C. E. Wilcox, P. C. Barbosa, and R. J. Strassman. 2015. Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Psychopharmacology* 29 (3):289–99. doi:10.1177/0269881114565144.
- Carhart-Harris, R. L., M. Bolstridge, J. Rucker, C. M. Day, D. Erritzoe, M. Kaelen, M. Bloomfield, J. A. Rickard, B. Forbes, A. Feilding, D. Taylor, S. Pilling, V. H. Curran, and D. J. Nutt. 2016. Psilocybin with psychological support

- for treatment-resistant depression: An open-label feasibility study. *Lancet Psychiatry* 3 (7):619–27. doi:10.1016/S2215-0366(16)30065-7.
- Carhart-Harris, R. L., D. Erritzoe, T. Williams, J. M. Stone, L. J. Reed, A. Colasanti, R. J. Tyacke, R. Leech, A. L. Malizia, K. Murphy, P. Hobden, J. Evans, A. Feilding, R. G. Wise, and D. J. Nutt. 2012. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proceedings of the National Academy of Sciences U S A* 109 (6):2138–43. doi:10.1073/pnas.1119598109.
- Cuthbert, B. N. 2015. Research domain criteria: Toward future psychiatric nosologies. *Dialogues in Clinical Neuroscience* 17 (1):89–97.
- Greicius, M. D., B. H. Flores, V. Menon, G. H. Glover, H. B. Solvason, H. Kenna, A. L. Reiss, and A. F. Schatzberg. 2007. Resting-state functional connectivity in major depression: Abnormally increased contributions from subgenual cingulate cortex and thalamus. *Biological Psychiatry* 62 (5):429–37. doi:10.1016/j.biopsych.2006.09.020.
- Griffiths, R. R., M. W. Johnson, M. A. Carducci, A. Umbricht, W. A. Richards, B. D. Richards, M. P. Cosimano, and M. A. Klinedinst. 2016. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of Psychopharmacology* 30 (12):1181–97. doi:10.1177/0269881116675513.
- Griffiths, R. R., W. A. Richards, U. McCann, and R. Jesse. 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology* 187 (3):268–83. doi:10.1007/s00213-006-0457-5.
- Grob, C. S., A. L. Danforth, G. S. Chopra, M. Hagerty, C. R. McKay, A. L. Halberstadt, and G. R. Greer. 2011. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of General Psychiatry* 68 (1):71–78. doi:10.1001/archgenpsychiatry.2010.116.
- Hasler, F., D. Bourquin, R. Brenneisen, T. Bär, and F. X. Vollenweider. 1997. Determination of psilocin and 4-hydroxyindole-3-acetic acid in plasma by HPLC-ECD and pharmacokinetic profiles of oral and intravenous psilocybin in man. *Pharmaceutica Acta Helveticae* 72 (3):175–84. doi:10.1016/S0031-6865(97)00014-9.
- Hasler, F., D. Bourquin, R. Brenneisen, and F. X. Vollenweider. 2002. Renal excretion profiles of psilocin following oral administration of psilocybin: A controlled study in man. *Journal of Pharmaceutical and Biomedical Analysis* 30 (2):331–39. doi:10.1016/S0731-7085(02)00278-9.
- Johnson, M. W., A. Garcia-Romeu, M. P. Cosimano, and R. R. Griffiths. 2014. Pilot study of the 5-HT_{2A} agonist psilocybin in the treatment of tobacco addiction. *Journal of Psychopharmacology* 28 (11):983–92. doi:10.1177/0269881114548296.
- Johnson, M. W., A. Garcia-Romeu, and R. R. Griffiths. 2016. Long-term follow-up of psilocybin-facilitated smoking cessation. *The American Journal of Drug and Alcohol Abuse* 43 (1):55–60.
- Kometer, M., A. Schmidt, R. Bachmann, E. Studerus, E. Seifritz, and F. X. Vollenweider. 2012. Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. *Biological Psychiatry* 72 (11):898–906. doi:10.1016/j.biopsych.2012.04.005.
- Lebedev, A. V., M. Lövdén, G. Rosenthal, A. Feilding, D. J. Nutt, and R. L. Carhart-Harris. 2015. Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. *Human Brain Mapping* 36 (8):3137–53. doi:10.1002/hbm.v36.8.
- Lindenblatt, H., E. Krämer, P. Holzmann-Erens, E. Gouzoulis-Mayfrank, and K. A. Kovar. 1998. Quantitation of psilocin in human plasma by high-performance liquid chromatography and electrochemical detection: Comparison of liquid-liquid extraction with automated on-line solid-phase extraction. *Journal of Chromatography B: Biomedical Sciences and Applications* 709 (2):255–63. doi:10.1016/S0378-4347(98)00067-X.
- Manevski, N., M. Kurkela, C. Höglund, T. Mauriala, M. H. Court, J. Yli-Kauhaluoma, and M. Finel. 2010. Glucuronidation of psilocin and 4-hydroxyindole by the human UDP-glucuronosyltransferases. *Drug Metabolism and Disposition* 38 (3):386–95. doi:10.1124/dmd.109.031138.
- McKenna, D. J., D. B. Repke, L. Lo, and S. J. Peroutka. 1990. Differential interactions of indolealkylamines with 5-hydroxytryptamine receptor subtypes. *Neuropharmacology* 29 (3):193–98. doi:10.1016/0028-3908(90)90001-8.
- Menon, V. 2011. Large-scale brain networks and psychopathology: A unifying triple network model. *Trends in Cognitive Sciences* 15 (10):483–506.
- Moreno, F. A., C. B. Wiegand, E. K. Taitano, and P. L. Delgado. 2006. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *Journal of Clinical Psychiatry* 67 (11):1735–40. doi:10.4088/JCP.v67n1110.
- Muthukumaraswamy, S. D., R. L. Carhart-Harris, R. J. Moran, M. J. Brookes, T. M. Williams, D. Erritzoe, B. Sessa, A. Papadopoulos, M. Bolstridge, K. D. Singh, A. Feilding, K. J. Friston, and D. J. Nutt. 2013. Broadband cortical desynchronization underlies the human psychedelic state. *The Journal of Neuroscience* 33 (38):15171–83. doi:10.1523/JNEUROSCI.2063-13.2013.
- Nagatomo, T., M. Rashid, H. A. Muntasir, and T. Komiyama. 2004. Functions of 5-HT_{2A} receptor and its antagonists in the cardiovascular system. *Pharmacology and Therapeutics* 104 (1):59–81. doi:10.1016/j.pharmthera.2004.08.005.
- Nichols, D. E. 2004. Hallucinogens. *Pharmacology and Therapeutics* 101 (2):131–81. doi:10.1016/j.pharmthera.2003.11.002.
- Nichols, D. E. 2016. Psychedelics. *Pharmacological Reviews* 68 (2):264–355. doi:10.1124/pr.115.011478.
- Nichols, D. E., M. W. Johnson, and C. D. Nichols. 2017. Psychedelics as medicines: An emerging new paradigm. *Clinical Pharmacology & Therapeutics* 101 (2):209–19.
- Passie, T., J. Seifert, U. Schneider, and H. M. Emrich. 2002. The pharmacology of psilocybin. *Addiction Biology* 7 (4):357–64. doi:10.1080/1355621021000005937.
- Pazos, A., A. Probst, and J. M. Palacios. 1987. Serotonin receptors in the human brain—III: Autoradiographic mapping of serotonin-1 receptors. *Neuroscience* 21 (1):97–122. doi:10.1016/0306-4522(87)90326-5.
- Quednow, B. B., M. Kometer, M. A. Geyer, and F. X. Vollenweider. 2012. Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by

- ketanserin in healthy human volunteers. *Neuropsychopharmacology* 37 (3):630–40. doi:[10.1038/npp.2011.228](https://doi.org/10.1038/npp.2011.228).
- Roseman, L., R. Leech, A. Feilding, D. J. Nutt, and R. L. Carhart-Harris. 2014. The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. *Frontiers in Human Neuroscience* 8:204. doi:[10.3389/fnhum.2014.00204](https://doi.org/10.3389/fnhum.2014.00204).
- Ross, S., A. Bossis, J. Guss, G. Agin-Liebes, T. Malone, B. Cohen, S. E. Mennenga, A. Belser, K. Kalliontzi, J. Babb, Z. Su, P. Corby, and B. L. Schmidt. 2016. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: A randomized controlled trial. *Journal of Psychopharmacology* 30 (12):1165–80. doi:[10.1177/0269881116675512](https://doi.org/10.1177/0269881116675512).
- Tylš, F., T. Páleníček, and J. Horáček. 2014. Psilocybin: Summary of knowledge and new perspectives. *European Neuropsychopharmacology* 24 (3):342–56. doi:[10.1016/j.euroneuro.2013.12.006](https://doi.org/10.1016/j.euroneuro.2013.12.006).
- Yu, A. M. 2008. Indolealkylamines: Biotransformations and potential drug-drug interactions. *The AAPS Journal* 10 (2):242–53. doi:[10.1208/s12248-008-9028-5](https://doi.org/10.1208/s12248-008-9028-5).