Data supplement for Fonzo et al., Psilocybin: From Psychiatric Pariah to Perceived Panacea. Am J Psychiatry (doi: 10.1176/appi.ajp.20230682)

Supplemental Results

Below is the list of publications included in this review as primary reports of acute and long-term primary clinical outcomes. We also note publications detailing secondary analyses that were identified for each primary report. Each bullet point represents a single independent clinical trial, with publications on the same bullet point line reflecting multiple reports of acute or long-term primary clinical outcomes. Indented beneath are reports of secondary analyses or secondary outcomes identified from each independent clinical trial.

- Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. The Journal of clinical psychiatry. 2006;67:1735-1740.
- Grob CS, Danforth AL, Chopra GS, Hagerty M, McKay CR, Halberstadt AL, Greer GR. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Archives of general psychiatry. 2011;68:71-78.
- Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. Journal of psychopharmacology (Oxford, England). 2014;28:983-992. Johnson MW, Garcia-Romeu A, Griffiths RR. Long-term follow-up of psilocybin-facilitated smoking cessation. The American journal of drug and alcohol abuse. 2017;43:55-60.
    - Garcia-Romeu A, Griffiths RR, Johnson MW. Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev. 2014;7:157-164

    - Strickland JC, Garcia-Romeu A, Johnson MW. Set and Setting: A Randomized Study of Different Musical Genres in Supporting Psychedelic Therapy. ACS Pharmacol Transl Sci. 2021;4:472-478.
- Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. Journal of psychopharmacology (Oxford, England). 2015;29:289-299.
- Griffiths RR, Johnson MW, Carducci MA, Umbricht A, Richards WA, Richards BD, Cosimano MP, Klinedinst MA. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. Journal of psychopharmacology (Oxford, England). 2016;30:1181-1197
- Ross S, Bossis A, Guss J, Agin-Liebes G, Malone T, Cohen B, Mennenga SE, Belser A, Kalliontzi K, Babb J, Su Z, Corby P, Schmidt BL. 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 (Oxford, England). 2016;30:1165-1180. Agin-Liebes GI, Malone T, Yalch MM, Mennenga SE, Ponté KL, Guss J, Bossis AP, Grigsby J, Fischer S, Ross S. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. Journal of psychopharmacology (Oxford, England). 2020;34:155-166.
    - Ross S, Agin-Liebes G, Lo S, Zeifman RJ, Ghazal L, Benville J, Franco Corso S, Bjerre Real C, Guss J, Bossis A, Mennenga SE. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. ACS Pharmacol Transl Sci. 2021;4:553-562
- Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D, Pilling S, Curran VH, Nutt DJ. Psilocybin with

psychological support for treatment-resistant depression: an open-label feasibility study. The Lancet Psychiatry. 2016;3:619-627. Carhart-Harris RL, Bolstridge M, Day CMJ, Rucker J, Watts R, Erritzoe DE, Kaelen M, Giribaldi B, Bloomfield M, Pilling S, Rickard JA, Forbes B, Feilding A, Taylor D, Curran HV, Nutt DJ. Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology (Berl). 2018;235:399-408

- Carhart-Harris RL, Roseman L, Bolstridge M, Demetriou L, Pannekoek JN, Wall MB, Tanner M, Kaelen M, McGonigle J, Murphy K, Leech R, Curran HV, Nutt DJ. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Scientific Reports. 2017;7:13187
- Lyons T, Carhart-Harris RL. More Realistic Forecasting of Future Life Events After Psilocybin for Treatment-Resistant Depression. Front Psychol. 2018;9:1721.
- Erritzoe D, Roseman L, Nour MM, MacLean K, Kaelen M, Nutt DJ, Carhart-Harris RL. Effects of psilocybin therapy on personality structure. Acta psychiatrica Scandinavica. 2018;138:368-378.
- Carrillo F, Sigman M, Fernández Slezak D, Ashton P, Fitzgerald L, Stroud J, Nutt DJ, Carhart-Harris RL. Natural speech algorithm applied to baseline interview data can predict which patients will respond to psilocybin for treatment-resistant depression. J Affect Disord. 2018;230:84-86.
- Roseman L, Nutt DJ, Carhart-Harris RL. Quality of Acute Psychedelic Experience Predicts Therapeutic Efficacy of Psilocybin for Treatment-Resistant Depression. Frontiers in pharmacology. 2017;8:974.
- Roseman L, Demetriou L, Wall MB, Nutt DJ, Carhart-Harris RL. Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. Neuropharmacology. 2018;142:263-269.

    - Stroud JB, Freeman TP, Leech R, Hindocha C, Lawn W, Nutt DJ, Curran HV, Carhart-Harris RL. Psilocybin with psychological support improves emotional face recognition in treatment-resistant depression. Psychopharmacology (Berl). 2018;235:459-466.
    - Mertens LJ, Wall MB, Roseman L, Demetriou L, Nutt DJ, Carhart-Harris RL. Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. Journal of psychopharmacology (Oxford, England). 2020;34:167-180
    - Shukuroglou M, Roseman L, Wall M, Nutt D, Kaelen M, Carhart-Harris R. Changes in music-evoked emotion and ventral striatal functional connectivity after psilocybin therapy for depression. Journal of psychopharmacology (Oxford, England). 2023;37:70-79.
- Anderson BT, Danforth A, Daroff PR, Stauffer C, Ekman E, Agin-Liebes G, Trope A, Boden MT, Dilley PJ, Mitchell J, Woolley J. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. EClinicalMedicine. 2020;27:100538.
    - Stauffer CS, Anderson BT, Ortigo KM, Woolley J. Psilocybin-Assisted Group Therapy and Attachment: Observed Reduction in Attachment Anxiety and Influences of Attachment Insecurity on the Psilocybin Experience. ACS Pharmacol Transl Sci. 2021;4:526-532.
- Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, Martell J, Blemings A, Erritzoe D, Nutt DJ. Trial of Psilocybin versus Escitalopram for Depression. New England Journal of Medicine. 2021;384:1402-1411.

    - Barba T, Buehler S, Kettner H, Radu C, Cunha BG, Nutt DJ, Erritzoe D, Roseman L, Carhart-Harris R. Effects of psilocybin versus escitalopram on rumination and thought suppression in depression. BJPsych Open. 2022;8:e163
    - Murphy R, Kettner H, Zeifman R, Giribaldi B, Kartner L, Martell J, Read T, Murphy-Beiner A, Baker-Jones M, Nutt D, Erritzoe D, Watts R, Carhart-Harris R. Therapeutic Alliance and Rapport Modulate Responses to Psilocybin Assisted Therapy for Depression. Frontiers in pharmacology. 2021;12:788155.
    - Daws RE, Timmermann C, Giribaldi B, Sexton JD, Wall MB, Erritzoe D, Roseman L, Nutt D, Carhart-Harris R. Increased global integration in the brain after psilocybin therapy for depression. Nat Med. 2022;28:844-851.
    - Nayak SM, Bari BA, Yaden DB, Spriggs MJ, Rosas FE, Peill JM, Giribaldi B, Erritzoe D, Nutt DJ, Carhart-Harris R. A Bayesian Reanalysis of a Trial of Psilocybin versus Escitalopram for Depression. Psychedelic Med (New Rochelle). 2023;1:18-26.
    - Zeifman RJ, Wagner AC, Monson CM, Carhart-Harris RL. How does psilocybin therapy work? An exploration of experiential avoidance as a putative mechanism of change. J Affect Disord. 2023;334:100-112.
    - Weiss B, Erritzoe D, Giribaldi B, Nutt DJ, Carhart-Harris RL. A critical evaluation of QIDS-SR-16 using data from a trial of psilocybin therapy versus escitalopram treatment for depression. Journal of psychopharmacology (Oxford, England). 2023;37:717-732.
- Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, Finan PH, Griffiths RR. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2021;78:481-489. Gukasyan N, Davis AK, Barrett FS, Cosimano MP, Sepeda ND, Johnson MW, Griffiths RR. Efficacy and safety of

psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. Journal of Psychopharmacology. 2022;36:151-158.

- von Rotz R, Schindowski EM, Jungwirth J, Schuldt A, Rieser NM, Zahoranszky K, Seifritz E, Nowak A, Nowak P, Jancke L, Preller KH, Vollenweider FX. Single-dose psilocybin-assisted therapy in major depressive disorder: A placebo-controlled, double-blind, randomised clinical trial. EClinicalMedicine. 2023;56:101809.
- Goodwin GM, Aaronson ST, Alvarez O, Arden PC, Baker A, Bennett JC, Bird C, Blom RE, Brennan C, Brusch D, Burke L, Campbell-Coker K, Carhart-Harris R, Cattell J, Daniel A, DeBattista C, Dunlop BW, Eisen K, Feifel D, Forbes M, Haumann HM, Hellerstein DJ, Hoppe AI, Husain MI, Jelen LA, Kamphuis J, Kawasaki J, Kelly JR, Key RE, Kishon R, Knatz Peck S, Knight G, Koolen MHB, Lean M, Licht RW, Maples-Keller JL, Mars J, Marwood L, McElhiney MC, Miller TL, Mirow A, Mistry S, Mletzko-Crowe T, Modlin LN, Nielsen RE, Nielson EM, Offerhaus SR, O'Keane V, Páleníček T, Printz D, Rademaker MC, van Reemst A, Reinholdt F, Repantis D, Rucker J, Rudow S, Ruffell S, Rush AJ, Schoevers RA, Seynaeve M, Shao S, Soares JC, Somers M, Stansfield SC, Sterling D, Strockis A, Tsai J, Visser L, Wahba M, Williams S, Young AH, Ywema P, Zisook S, Malievskaia E. Single-Dose Psilocybin for a Treatment-Resistant Episode of Major Depression. New England Journal of Medicine. 2022;387:1637-1648. Goodwin GM, Aaronson ST, Alvarez O, Atli M, Bennett JC, Croal M, DeBattista C, Dunlop BW, Feifel D, Hellerstein DJ, Husain MI, Kelly JR, Lennard-Jones MR, Licht RW, Marwood L, Mistry S, Palenicek T, Redjep O, Repantis D, Schoevers RA, Septimus B, Simmons HJ, Soares JC, Somers M, Stansfield SC, Stuart JR, Tadley HH, Thiara NK, Tsai J, Wahba M, Williams S, Winzer RI, Young AH, Young MB, Zisook S, Malievskaia E. Single-dose psilocybin for a treatment-resistant episode of major depression: Impact on patient-reported depression severity, anxiety, function, and quality of life. J Affect Disord. 2023;327:120-127.

    - Dougherty RF, Clarke P, Atli M, Kuc J, Schlosser D, Dunlop BW, Hellerstein DJ, Aaronson ST, Zisook S, Young AH, Carhart-Harris R, Goodwin GM, Ryslik GA. Psilocybin therapy for treatment resistant depression: prediction of clinical outcome by natural language processing. Psychopharmacology (Berl). 2023.
- Bogenschutz MP, Ross S, Bhatt S, Baron T, Forcehimes AA, Laska E, Mennenga SE, O'Donnell K, Owens LT, Podrebarac S, Rotrosen J, Tonigan JS, Worth L. Percentage of Heavy Drinking Days Following Psilocybin-Assisted Psychotherapy vs Placebo in the Treatment of Adult Patients With Alcohol Use Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2022;79:953-962.
- Heinzerling KG, Sergi K, Linton M, Rich R, Youssef B, Bentancourt I, Bramen J, Siddarth P, Schwartzberg L, Kelly DF. Nature-themed video intervention may improve cardiovascular safety of psilocybin-assisted therapy for alcohol use disorder. Frontiers in psychiatry. 2023;14:1215972.
- Raison CL, Sanacora G, Woolley J, Heinzerling K, Dunlop BW, Brown RT, Kakar R, Hassman M, Trivedi RP, Robison R, Gukasyan N, Nayak SM, Hu X, O'Donnell KC, Kelmendi B, Sloshower J, Penn AD, Bradley E, Kelly DF, Mletzko T, Nicholas CR, Hutson PR, Tarpley G, Utzinger M, Lenoch K, Warchol K, Gapasin T, Davis MC, Nelson-Douthit C, Wilson S, Brown C, Linton W, Ross S, Griffiths RR. Single-Dose Psilocybin Treatment for Major Depressive Disorder: A Randomized Clinical Trial. JAMA. 2023;330:843-853.
- Peck SK, Shao S, Gruen T, Yang K, Babakanian A, Trim J, Finn DM, Kaye WH. Psilocybin therapy for females with anorexia nervosa: a phase 1, open-label feasibility study. Nat Med. 2023;29:1947-1953.
- Goodwin GM, Croal M, Feifel D, Kelly JR, Marwood L, Mistry S, O'Keane V, Peck SK, Simmons H, Sisa C, Stansfield SC, Tsai J, Williams S, Malievskaia E. Psilocybin for

treatment resistant depression in patients taking a concomitant SSRI medication. Neuropsychopharmacology. 2023;48:1492-1499.

- Lewis BR, Garland EL, Byrne K, Durns T, Hendrick J, Beck A, Thielking P. HOPE: A Pilot Study of Psilocybin Enhanced Group Psychotherapy in Patients With Cancer. J Pain Symptom Manage. 2023;66:258-269.
- Agrawal M, Emanuel E, Richards B, Richards W, Roddy K, Thambi P. Assessment of Psilocybin Therapy for Patients With Cancer and Major Depression Disorder. JAMA Oncol. 2023;9:864-866. Shnayder S, Ameli R, Sinaii N, Berger A, Agrawal M. Psilocybin-assisted therapy improves psycho-social-spiritual well-being in cancer patients. J Affect Disord. 2023;323:592-597.
- Schneier FR, Feusner J, Wheaton MG, Gomez GJ, Cornejo G, Naraindas AM, Hellerstein DJ. Pilot study of single-dose psilocybin for serotonin reuptake inhibitor-resistant body dysmorphic disorder. J Psychiatr Res. 2023;161:364-370.
- Sloshower J, Skosnik PD, Safi-Aghdam H, Pathania S, Syed S, Pittman B, D'Souza DC. Psilocybin-assisted therapy for major depressive disorder: An exploratory placebo-controlled, fixed-order trial. Journal of psychopharmacology (Oxford, England). 2023;37:698-706.
    - Skosnik PD, Sloshower J, Safi-Aghdam H, Pathania S, Syed S, Pittman B, D'Souza DC. Sub-acute effects of psilocybin on EEG correlates of neural plasticity in major depression: Relationship to symptoms. Journal of psychopharmacology (Oxford, England). 2023;37:687-697.

Supplemental Review

Psilocybin Pharmacology and Effects in Humans

Pharmacokinetics

Psilocybin is an indolylalkylamine (O-phosphoryl-4-hydroxy-N,N-dimethyl-tryptamine) prodrug that is rapidly dephosphorylated upon ingestion by stomach acid or intestinal alkaline phosphatase to its active metabolite, psilocin (4-hydroxy-N,N-dimethyltryptamine)(1). Psilocin is a lipophilic compound, readily crossing the blood-brain barrier, and is the chemical moiety responsible for the psychoactive effects of psilocybin. In natural form (fresh or dried mushrooms), psilocybin is present in a four-times larger quantity than the active metabolite, psilocin. By the time psilocybin is orally ingested and reaches the intestinal tract, it is primarily in the form of psilocin, where it is readily absorbed by the intestine and found to almost uniformly distribute throughout the body (1). Psilocin is detectable in human plasma within 20-40 minutes after oral ingestion, and maximum concentration is reached in about 80-100 minutes. The active metabolite and its breakdown products are excreted through urine and feces, though renal clearance accounts for a minority of drug excretion in humans. Very little psilocin is detectable in urine 24 hours after ingestion. However, psilocin hydrolysis products, primarily psilocin-O-glucuronide, are more readily detectable in urine following ingestion and are detectable for a longer period due to their increased stability (2).

Pharmacodynamics

Although all classical psychedelic compounds are generally accepted to primarily act through functionally-selective agonism of the serotonin (5-HT) 2A receptor (recruiting, to a greater extent, certain downstream signaling pathways), the indoleamine psychedelics such as psilocybin/psilocin, N,N-dimethyltryptamine (DMT), and lysergic acid diethylamide (LSD) are far from selective (3). These compounds have substantial binding affinity for many 5-HT receptors. In addition to the 5-HT_{2A} receptor, psilocin demonstrates substantial binding affinities for the 5-

HT_{2B}, 5-HT_{2C}, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, and 5-HT_7 receptors. Psilocin also displays a relatively high affinity for the histamine H1 receptor and a more moderate affinity for the alpha-adrenergic 2A and 2B receptors (3). However, because the relatively 5-HT_2 non-selective indoleamine psychedelics demonstrate qualitatively similar effects and cross-tolerance to phenylalkylamine psychedelics such as mescaline that are much more selective for 5-HT_2 receptors, these substances are all believed to act through a common 5-HT_2 receptor-mediated mechanism. There are additional lines of evidence for the key importance of 5-HT_{2A} receptors in mediating the effects of psilocin and other psychedelics. First, the subjective psychedelic effects of psilocybin, as well as its effects on automatic and controlled inhibitory processes, visual phenomena, mood, and processing of emotional stimuli, are blocked dose-dependently by ketanserin (4-7), a potent 5-HT_{2A} and H1 receptor antagonist, with more moderate antagonist activity at 5-HT_{2C} receptors, alpha-adrenergic 1A/1B receptors, and the vesicular monoamine transporter (8, 9). However, the diminishment of attentional capacity, as well as slowing of binocular rivalry (a perceptual switching between awareness of two simultaneously presented images) by psilocybin, was not blocked by co-administration of ketanserin in healthy individuals, suggesting that at least some of its cognitive and subjective effects are mediated via other receptor mechanisms, such as 5-HT_{1A} receptors (10, 11). Second, administration of psilocybin was shown to result in dose-dependent occupancy of 5-HT_{2A} receptors using positron emission tomography (PET), and greater occupancy and plasma psilocin levels were both associated with more intense subjective psychedelic effects (12, 13). Combined with preclinical studies, these findings strongly suggest that the activation of pathways downstream from the 5-HT_{2A} receptor by psilocin is necessary to induce many of the prototypical psychedelic effects. However, activation of the 5-HT_{2A} receptor is insufficient to induce a psychedelic experience, as several known compounds (e.g., lisuride and ergotamine) share similar structural properties and bind to the 5-HT_{2A} receptor but do not produce psychoactive effects. Evidence indicates that downstream divergent signaling cascades that occur after activation of the 5-HT_{2A} receptor may differentiate psychedelic from non-psychedelic

5-HT_{2A} agonists, but the precise cellular mechanisms underlying the unique psychedelic state in humans remain poorly understood (14, 15). Taken together, the pharmacodynamics of psilocin and other psychedelic compounds remain coarsely characterized, particularly regarding the processes occurring after 5-HT_{2A} receptor binding, how such processes may lead to the prototypical behavioral and subjective psychedelic effects and downstream potential therapeutic effects in humans and animals, and how these processes differ from those of other 5-HT_{2A} agonists that do no induce subjective alterations in consciousness.

Acute and Post-Acute Physiological, Subjective, Psychological, and Cognitive Effects

When ingested, psilocybin induces a broad array of powerful subjective, physiological, psychological, and cognitive effects beginning within 20-40 min of administration and lasting for up to 6 hours afterwards. Qualitatively, subjective effects are similar to those of other 5-HT_{2A} agonist psychedelics, such as lysergic acid diethylamide (LSD) (16) and mescaline, and include a complex and variable array of changes. Intensity of effects is typically dose dependent, with higher doses producing more intense and longer-lasting alterations in consciousness (16). These include alterations in basic sensory processing, such as visual, auditory, and tactile phenomena, sometimes including visual/auditory distortions, illusions, and hallucinations as well as synesthesia; changes in interoceptive processing of body sensations and alteration in body awareness; alterations in intensity of emotional experience, ranging from more intense emotional states to emotional blunting; alterations in quality of emotional experience and mood, ranging from serenity, euphoria, bliss, and deep peace to anxiety, paranoia, and agitation; and increased and/or decreased energy level and psychomotor activity (17). Physiological effects typically include an increase in heart rate, blood pressure, and body temperature, with psilocybin tending to promote greater increases in blood pressure and body temperature but lower increases in heart rate relative to LSD and placebo, as demonstrated in a double-blind, randomized, placebo-controlled, crossover design in (N=28) healthy individuals administered placebo, 15mg psilocybin,

30 mg psilocybin, 100 µg LSD, and 200 µg LSD in separate sessions (16). Additional physiological effects noted in this study were pupillary dilation, disruption of normal light-induced constriction of pupil size, and increasing concentrations of plasma cortisol, prolactin, and oxytocin. Additional alterations are generally noted in complex mental phenomena, such as a general loosening of cognitive processes resulting in less linear and more fluid, creative, and associative thought processes; and alterations in perception of self, time, and space, including a lessening of the normally-rigid demarcation between self, other, and environment (18). Such experiences are typically retrospectively described as “pleasurable”, “beautiful”, or “magic(al)”, but can also be perceived as anxiety-provoking or harrowing by some individuals (18). Under optimum conditions, the reduction in subjective demarcation of the self can be perceived with a noetic and emotional quality that leads to insightful spiritual revelations, previously described as “touching” or “unifying with a higher reality” (18). Such experiences, often termed “mystical-type” experiences due to qualitative similarities with subjective states reported in religious and spiritual texts, can have profound personal meaning to the individual and may promote longer-term positive benefits (19-22).

Numerous self-report measures have been constructed to measure the subjective acute effects of psychedelic substances, many of which have been investigated in relation to psilocybin administration. These include the Altered States of Consciousness Scale (ASC) (23), which has gone through several versions and iterations (24), but is now most commonly utilized in a visual analogue form known as the 5 Dimensional ASC (5D-ASC)(25). This measure has 11 subscales (experience of unity, spiritual experience, blissful state, insightfulness, disembodiment, impaired control and cognition, anxiety, complex imagery, elementary imagery, audio-visual synesthesia, and changed meaning of perception) and 5 key-dimensions composed of these subscales (oceanic boundlessness, anxious ego dissolution, visionary restructuralization, auditory alterations, and reduction of vigilance), of which the oceanic boundless dimension is frequently utilized as a standardized measure of “mystical-type” experiences occasioned by a psychedelic

compound. Others include the Hallucinogen Rating Scale (HRS), a 99-item questionnaire designed by Strassman to show sensitivity to the psychedelic dimethyltryptamine (26-28) and consisting of six subscales (intensity, somaesthesia, affect, perception, cognition, and volition); and the Pahnke-Richards Mystical Experience Questionnaire (MEQ)(29), a measure derived from selected items of the 100-item States of Consciousness Questionnaire (SOCQ)(19) that is based upon the work of Stace (30) in defining common dimensions of mystical-type experiences across cultures and time periods. It is now most frequently administered in a 30-item form, known as the MEQ-30 (31), which was validated on individuals undergoing psilocybin administration in a research context. Psilocybin administered to healthy volunteers has been demonstrated to produce elevations across all total and subscale scores of the HRS (17, 19, 21), ASC (17-19, 21), and MEQ-30 (19, 21), demonstrating consistent sensitivity of these measures to the effects of psilocybin, particularly in comparison to inactive placebo (17, 18) and methylphenidate (19). Interestingly, in a within-subjects, repeated-measures, dose-escalation design in healthy individuals (N=12) administered psilocybin in doses of 0.3 mg/kg, 0.45 mg/kg, and 0.6 mg/kg, MEQ-30 scores did not show a clear dose-dependent relationship, nor were rates of mystical experience different across dose levels (32). In relation to dextromethorphan (DXM; an NMDA receptor antagonist with psychoactive properties similar to dissociative anesthetics such as ketamine and phencyclidine), psilocybin produced similar changes in intensity of drug effect, psychomotor function, and some measures of emotion, but it produced greater feelings of joy/intense happiness, less nausea/vomiting, more yawning and tearing/crying, more intense/profound visual effects, greater absorption in music, less disembodiment, and a greater experience of mystical-type phenomena as measured by 5D-ASC, HRS, and MEQ (33). These latter findings highlight initial evidence for class-specificity of 5-HT_{2A} agonist psychedelics in producing mystical-type experiences, but comparisons of psilocybin or other 5-HT_{2A} agonist psychedelics vs. other hallucinogenic compounds operating via unique pathways (e.g., ketamine, salvinorin A) are sparse and require further investigation.

Numerous laboratory investigations have provided evidence regarding the effects of psilocybin on sensory, psychological, and cognitive processes. Early work examined psilocybin as a pharmacological probe to induce acute schizophrenia-like deficits in cognitive/sensory processes in healthy individuals (5, 6, 10, 34-37). In the sensory processing domain, one study examining inhibition of the startle reflex, known as prepulse inhibition (a putative measure of sensorimotor gating capacity, often found to be deficient in human and animal models of schizophrenia and to be diminished in animals following administration of psychedelics), demonstrated that psilocybin unexpectedly increased prepulse inhibition in healthy volunteers (N=6) relative to placebo (N=6) but had no effect on startle habituation (34). This effect was later shown to be dependent on the interstimulus interval, with psilocybin dose-dependently reducing prepulse inhibition in healthy individuals (N=16) in a repeated-measures, counterbalanced, placebo-controlled, dose-response design at short (30ms) intervals, having no effect on medium (60ms) intervals, and actually increasing prepulse inhibition at long intervals (120-2000 ms)(38). The prepulse inhibition deficit at short intervals was likewise positively correlated with the degree of psilocybin-induced impairment in sustained attention. A later study in healthy individuals (N=16) replicated this same effect of psilocybin attenuation of prepulse inhibition at short intervals (30ms) and also demonstrated that pre-administration of ketanserin blocked this effect and had no effect by itself (6). A later study examined psilocybin's effects on motion perception in healthy individuals demonstrated that psilocybin selectively impaired perception of visual phenomena mediated by high-level but not low-level global motion detectors (37), demonstrating a specific effect on one aspect of visual sensory processing. Another component of visual processing, binocular rivalry (in which two images are presented simultaneously to corresponding points in the left and right eyes) will typically induce perceptual alterations between focus on each of the images. In healthy individuals (N=12) administered placebo, a low dose of psilocybin, and a high dose of psilocybin in a within-subject repeated-measures design, psilocybin was shown in both low and high dose conditions to reduce the rate and rhythmicity of perceptual alterations at the peak of drug action

(90 min post administration), which later returned to normal (or even higher than baseline) by the time subjective effects had ceased (360 min post-administration)(39). This effect on binocular rivalry was later shown to be resistant to administration of ketanserin in healthy individuals (N=10), which suggests psilocybin effects on binocular rivalry are not mediated by ketanserin-antagonized receptors (primarily 5-HT_{2A} but also 5-HT_{2C}) and occur via a different receptor binding process.

Another study examining orienting of spatial attention demonstrated that healthy individuals administered psilocybin (N=8) demonstrated prolonged attentional orienting reaction times and specific deficits in disengagement of attention relative to another psychoactive substance, methylenedioxyethylamphetamine (MDEA; N=8), a substance similar in structure and effect to methylenedioxymethamphetamine (MDMA), but not methamphetamine (N=8) (35). A follow-up study extended this finding by demonstrating that psilocybin reduced spatial tracking ability but not spatial working memory performance in healthy individuals (N=8), and this effect was not ameliorated by administration of the 5-$HT_{2A/2C}$ antagonist, ketanserin (10). This suggests psilocybin induces an acute deficit in spatial processing and spatial attention also not mediated by 5-$HT_{2A/2C}$ receptors, which was theorized to be mediated by 5-HT_{1A} agonism and to reflect a reduced ability to suppress or ignore distracting stimuli rather than a deficit in attentional capacity, *per se*. Psilocybin likewise induced deficits on performance in a continuous performance task (N=18) in a within-subject, placebo-controlled, counterbalanced design (36), demonstrating an acute impairment of processing performance in another attentional domain that may be mediated via a similar difficulty in inhibiting distracting information. Controlled inhibition, however, as assessed by performance of a Stroop paradigm in healthy individuals (N=16) administered psilocybin either with or without ketanserin pre-administration demonstrated that psilocybin did impair performance on the Stroop paradigm (both in terms of response latencies and number of errors), but this effect was removed by ketanserin pre-administration (6). Thus, while some of the detrimental effects of psilocybin on attentional control appear to be independent of 5-$HT_{2A/2C}$ receptor activation, effects on more deliberate or controlled inhibitory processes (as well as

automatic inhibition, as evidenced by aforementioned findings of psilocybin effects on prepulse inhibition) do appear to be mediated via psilocybin activity at this group of receptors. The effects of psilocybin on higher-order cognitive processes such as associative learning and executive function were tested in a within-subject, double-blind, dose-response framework (10, 20, and 30 mg of psilocybin/70kg) in healthy individuals (N=20) vs. both placebo and 400mg/70kg DXM, a psychoactive drug comparator condition (40). Psilocybin was found to not induce global cognitive impairment (as measured by the mini mental status examination), but it did produce psychomotor slowing across all doses and dose-dependently reduced working memory and performance on measures of associative learning (manifested as spared accuracy but slower performance, perhaps indicative of an attention or working memory impairment-induced speed/accuracy tradeoff). Notably, psilocybin was found in this study to spare function on measures of episodic memory, response inhibition, and executive function that were impaired by DXM. Consistent with an acute impairment of cognitive functions, psilocybin (0.17mg/kg) administration was also found to impair performance on laboratory measures of creative thinking in healthy individuals (N=19) in a double-blind, placebo-controlled, parallel-group design, despite the fact that it increased self-reported measures of creative cognition acutely and promoted an increase in novel ideas 7 days afterwards (41). This latter finding is also consistent with a report examining cognitive flexibility (performance on a set-shifting task) in an open-label psilocybin treatment study of patients with major depressive disorder (N=24), which observed that cognitive flexibility was increased for at least 4 weeks post-treatment (42). However, findings from a large randomized, double-blind, placebo-controlled, parallel-arm trial of 10 or 25mg psilocybin administered to healthy participants simultaneously in up to 6 participants at a time (N=89) produced equivocal evidence for any changes in cognitive function 1 week to 1 month following drug administration (43).

Time perception and the temporal control of behavior is a process that links sensory, motor, and cognitive processes, and it has also been investigated in relation to psilocybin administration, congruent with the subjective reports for altered perception of time while

experiencing the effects of this drug (44, 45). In healthy volunteers (N=12) in a within-subject, placebo-controlled, double-blind design, psilocybin was found to impair participants' ability to reproduce time intervals longer than 2.5 sec, impair synchronization to inter-beat intervals longer than 2 sec, and slow down the preferred tapping rate of participants (44). These changes were observed alongside subjective reports for changes in the perceived sense of time.

Consistent with the profound effects of psilocybin on affect and emotion, the acute effects of psilocybin on the processing of socioemotional stimuli have also been investigated in laboratory settings. In a within-subject, double-blind, placebo-controlled study, healthy individuals (N=17) administered psilocybin or placebo with or without ketanserin observed that psilocybin decreased accuracy of identification of negative emotional faces, an effect which was abolished alongside ketanserin pre-administration (5). However, in this same study, psilocybin also promoted an enhanced response bias to positive word stimuli (as evidenced by a selective prolongation of reaction times for negative vs. positive stimuli in an emotional go-no/go paradigm) which remained even alongside ketanserin pre-administration. The effects of psilocybin on another aspect of socioemotional processing, empathy, was investigated in a laboratory setting in healthy individuals (N=33) through administration of the Multifaceted Empathy Test (46), a test utilizing photorealistic stimuli of individuals in emotionally-charged situations and querying for aspects of cognitive and emotional empathy, in a double-blind, placebo-controlled, within-subject design (47). Psilocybin administration was found to increase emotional, but not cognitive, empathy, and it furthermore demonstrated no effect on moral decision-making during moral dilemmas, a high-level process also incorporating elements of emotion processing, empathy, and complex cognition. Consistent with these data, psilocybin was also found to reduce rejection of "unfair" offers during the Ultimatum Game (a popular laboratory paradigm utilized to probe processing of social norm violations through acceptance or rejection of a portion of a share of money allocated to two players, one of which proposes a split to the other) when assessed after many of the acute psychedelic effects of 0.2 mg of intravenous psilocybin in healthy volunteers (N=19) had

dissipated (48). The authors interpreted this as evidence that psilocybin alters the conceptualization of “social reward”, emphasizing interaction and cooperation over punishing social norm violations, which would be consistent with the idea that psilocybin increases empathy and enhances processing of positive emotional stimuli. Findings are limited, however, by the single-arm open-label design of this study. Lastly, consistent with cognitive effects, longer-term beneficial or detrimental effects of psilocybin on emotion processing and mood in healthy individuals (N=89) administered 10 or 25mg of psilocybin were absent 1 week following drug administration (43), which further highlights the predominant pattern of substantial acute changes in perceptual, cognitive, and emotional function following psilocybin administration that diminish and are relatively absent days to weeks afterward in healthy individuals.

Acute Neurobiological Effects

Brain imaging studies examining the acute effects of psilocybin administration began to populate the scientific literature in the late 1990’s, beginning with a positron emission tomography [F-18]fluorodeoxyglucose (FDG-PET) study examining regional cerebral glucose metabolism, a metabolic marker of brain activity, in healthy individuals (N=10) administered a 15-20mg dose of psilocybin (49). Psilocybin was found to globally increase metabolic rate in the brain. The highest increases were in the frontal lobes and medial temporal lobes, which also positively correlated with the “hallucinatory ego disintegration” effects of the drug. A later FDG-PET study replicated this frontotemporal hypermetabolism in healthy individuals (N=8) and also observed hypometabolism in the thalamus (50). Later investigations have utilized arterial spin labeling (ASL), a magnetic resonance imaging (MRI)-derived marker of cerebral blood flow, and blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) to investigate the acute effects of psilocybin on resting brain function. In a within-subject, placebo-controlled design, healthy individuals (N=15) received intravenously 2 mg of psilocybin in saline or saline alone while undergoing MRI scanning (51). ASL, here calculated as a measure of global

cerebral blood flow (gCBF), showed widespread reductions across cortical and subcortical brain areas, including the thalamus, ventromedial prefrontal cortex (vmPFC), lateral prefrontal cortex (lPFC), posterior medial cortices (posterior cingulate/precuneus), and parietal cortices. Greater decreases in gCBF were associated with more intense subjective drug effects. A later study examining a larger sample of healthy individuals (N=58) with a low (0.16 mg/kg) and high dose (0.215 mg/kg) of psilocybin (N=29 each) examined both ASL-measured gCBF as well as relative CBF (rCBF), which adjusts the local gCBF for the change in CBF across the brain as a whole (52). Although the gCBF measurements replicated earlier findings for decreases in blood flow across frontal, temporal, parietal, and subcortical structures, rCBF demonstrated a relative increase in blood flow in right frontal and temporal areas and a relative decrease in blood flow in left hemisphere parietal, occipital, and subcortical structures. These findings thus converge with FDG-PET studies to suggest psilocybin induces a hyperfrontal metabolic state, but this is characterized by less of a relative decrease in overall cerebral blood flow across the brain.

BOLD fMRI studies have demonstrated that, similar to gCBF, the brain at rest is characterized by a general decrease in activation from before to after psilocybin infusion. In healthy individuals (N=15), psilocybin intravenous infusion resulted in decreased BOLD signal in the vmPFC and posterior cingulate cortex, key nodes of the brain's default mode network (DMN)(53), as well as the thalamus, medial temporal lobes, and striatum. In this same sample, psilocybin likewise decreased connectivity of the vmPFC with the posterior cingulate and increased connectivity of the vmPFC with lateral frontal regions implicated in executive control (51), which was the first observation for the now well-replicated effect of psilocybin reducing connectivity within canonical resting state networks (e.g., DMN) and increasing connectivity between brain regions of normally-segregated resting state networks (e.g., DMN and the frontoparietal control network, also known as the task positive network). A subsequent re-analysis of these data on the level of whole networks broadened this finding to demonstrate increased between-network connectivity between the DMN and the task positive network, which are typically

well-segregated in the brain at rest (54). This study also produced evidence for increased connectivity between the task positive network and the thalamus with a trend towards increased connectivity between the thalamus and DMN, which is consistent with a popular neurobiological model postulating psychedelic compounds produce their well-known effects via effects on cortico-striato-thalamo-cortical loops (55). A more extensive investigation of connectivity within and between networks in this same sample observed a widespread increase in connectivity between normally segregated resting state networks under the influence of psilocybin that was not limited to the DMN or task positive network and also included increased connectivity between additional higher-order heteromodal networks (e.g., dorsal attention network) and unimodal (e.g., visual, auditory, somatomotor) sensory networks (56). These increases in between-network connectivity produced by psilocybin were compared to effects produced by MDMA vs. placebo in a separate sample and were not observed (except for increased connectivity between the DMN and executive control network). However, psilocybin also produced decreases in connectivity between unimodal sensory networks (somatomotor and visual), which may be secondary to the increased connectivity between higher order heteromodal and unimodal sensory networks. A subsequent study in healthy individuals (N=15) examined the relationship of psilocin plasma levels and subjective drug intensity to resting state network connectivity changes and likewise observed that both psilocin plasma levels and drug intensity were associated with greater reduction of within-network connectivity metrics (particularly the DMN and salience network) and greater increases in between-network connectivity measures (57). Similar widespread network reorganization effects are seen for other 5-HT_{2A} agonist psychedelics, such as LSD and ayahuasca (58, 59). These findings were interpreted to suggest that the complex visual and sensory phenomena that characterize the psychedelic experience may arise, in part, due to the increased connectivity promoted between normally well-segregated heteromodal and unimodal sensory cortical networks (56).

In contrast, an investigation of intravenous psilocybin-induced acute connectivity changes (N=15) in relation to subjective effects characterized by the experience of ego-dissolution produced evidence that reduced connectivity between the anterior parahippocampal cortices, located in the medial temporal lobe adjacent to the hippocampus and implicated in memory and contextual processing, and higher-order cortical areas was specifically associated with the subjective sense of loss of the normally readily-apparent ego sense (60). Additional analyses revealed ego loss was associated with a functional disconnection of the medial temporal lobe, more generally, with higher-order frontal and parietal cortical areas, as well as a reduction in connectivity within the salience network (60), which is critically implicated in the selection of stimuli deserving of conscious attention (61). Thus, the functional disconnection of more primitive cortical structures in the medial temporal lobe from higher-order cortical substrates as well as less coordinated function within networks critical for attentional control may be facets of psilocybin's effects that uniquely contributes to the "ego dissolving" characteristics of the psychedelic experience, whereas the heightened sensory and visual phenomena may be more specific to connectivity changes between frontal/parietal heteromodal and unimodal sensory cortices.

The functional connectivity of a relatively understudied subcortical portion of the brain, known as the claustrum, has also been examined in relation to acute psilocybin administration. The claustrum is a thin strip of gray matter located between the insular cortex and putamen in each brain hemisphere that maintains broad bi-directional connections with most all of the cortical mantle (62). It has been proposed to serve a functional role as a subcortical integrator of multiple sensory modalities through serving to synchronize or coordinate the function of cortical areas, though its precise function remains a subject of debate (62). It has been observed to activate at the onset of a cognitively-demanding task and to display connectivity with most areas of the default mode and executive control networks, giving rise to the hypothesis that it is particularly important in subserving high-level cognitive functions (63). Evidence in rats also indicates the claustrum expresses 5-HT_{2A} receptors (64), suggesting it may be one of many sites of action for

psilocybin. In a sample of healthy individuals (N=15) using a placebo-controlled, repeated measures design, 10mg/70kg of psilocybin acutely promoted lateralized changes in claustrum functional connectivity (65). For the right claustrum, connectivity with auditory and default mode networks was reduced and connectivity with the frontoparietal control network was increased, but for the left claustrum, connectivity with the frontoparietal control network was decreased. For both left and right claustrum, psilocybin attenuated the degree of BOLD signal variance and amplitude of fluctuations, both measures of resting-state regional activity. Thus, psilocybin does exert changes on claustrum activity and functional connectivity patterns, particularly in association with large-scale cortical networks. These findings thus highlight another potential candidate mechanism of psychedelic effects that implicate cortical and subcortical desynchronization.

Task-based fMRI has also been utilized to examine how psilocybin acutely impacts the function or cortical and subcortical structures. The first such study examined in how 2mg IV psilocybin vs. saline impacted autobiographical memory recollection to verbal cues in 15 healthy individuals in a within-subjects, repeated measures design (66). The authors observed that psilocybin increased self-reported vividness and visual imagery during autobiographical memory recall and increased brain activation in the late phases of recall in primary somatosensory and visual cortices, which was interpreted to be one potential neurobiological mechanism underlying the increased realistic quality of memories that is sometimes reported under the influence of psychedelics (67). Subsequent studies examined the acute effects of psilocybin on facial emotion processing, which is a popular behavioral probe of affective neurocircuitry function. These studies have focused on the amygdala, in particular, due to its prominent role in neurocircuitry models of depression (68) and anxiety (69) and its demonstrated role in fear (70) and negative emotion (71). In a randomized, double-blind, placebo-controlled crossover design, 25 healthy participants received 0.16mg/kg of oral psilocybin or inactive placebo underwent fMRI on two separate occasions while completing a facial emotion discrimination paradigm (72). Psilocybin was found to attenuate right amygdala activation to both negative and neutral facial emotions, with a similar

trend in the left amygdala. Additional attenuations in activation were noted in secondary face processing areas of the extended visual system. Interestingly, a greater attenuation of right amygdala activation to negative facial emotions was associated with a larger improvement in positive affect. Similar psilocybin-induced attenuations of activity in subcortical and visual sensory processing areas to facial emotional stimuli have also been observed using EEG and source localization procedures (73). A later study examined fMRI connectivity, or coordinated function over time, of the amygdala with other areas of the brain during emotional face discrimination in 18 healthy volunteers in a double-blind, placebo-controlled, cross-over design and observed decreased amygdala connectivity with frontal and striatal areas (74), which is consistent with prior activation findings suggesting that psilocybin both dampens amygdala activity and attenuates communication with its typical connectivity targets. A double-blind, placebo-controlled, crossover study of psilocybin (0.215 mg/kg) vs. placebo also examined social exclusion in 21 healthy individuals during fMRI using a popular behavioral paradigm and observed that neural responses to social exclusion were attenuated by psilocybin in areas of the dorsal cingulate and dorsolateral prefrontal cortex, cortical areas that are typically activated by the experience of painful stimuli, including social rejection (75). Moreover, psilocybin also attenuated the subjective intensity of social exclusion in these participants. Thus, it is reasonable to surmise that some of the aforementioned functional changes in cortical and subcortical circuitry may underlie psilocybin's acute effects on emotion, affect, and mood, but more extensive research in larger samples and under a broader array of affective contexts is needed.

Persisting Neurobiological Effects

A longer-term open-label, within-subject repeated measures pilot study in 12 healthy volunteers examined the effects of 25mg/70kg of oral psilocybin on emotions and brain function at 1 week and 1-month post-administration and observed that psilocybin attenuated bilateral amygdala responses to facial emotional stimuli at 1 week, but this effect disappeared by 1 month

post-administration (76). Additional effects were observed at 1 week, including reduction in negative affect, increases in positive affect, increased prefrontal cortical responses to stimuli evoking emotional conflict, and predominantly increased resting state connectivity amongst various regions that did not follow a discernible network pattern. These effects largely abated one-month post-administration, except for the increases in positive affect and some increases in resting state connectivity, which remained. This study represents the first investigation of the potential longer-term enduring effects of a single administration of psilocybin on brain function in healthy individuals, producing initial evidence for functional changes that persist at least a week following the administration. A later study examined potential persisting neurobiological changes following psilocybin administration on an even longer time scale (1 week and 3 months)(77). Ten healthy individuals received 0.2-0.3mg/kg of oral psilocybin in an open-label design, and only one facet of connectivity was found to be changed at 1 week (but not 3 months) post-psilocybin. This was decreased connectivity amongst nodes of the executive control network at 1 week, which was absent by the 3-month follow-up. Thus, the present findings suggest that, in healthy individuals, some neurobiological changes related to psilocybin are measurable at 1 week and up to 1-month post-administration, but any longer-term changes that may occur beyond that time frame will require more sensitive instrumentation and/or larger samples to reliably capture.

Neuroimaging studies in clinical populations (at present, primarily MDD) have primarily focused on measuring short and longer-term neurobiological changes on the scale of one day to one-week post-administration due to the added difficulty of measuring acute psilocybin effects in patients undergoing psilocybin administration for therapeutic purposes. These findings have revealed that, at 1 day post-administration, 19 individuals with MDD demonstrated reduced cerebral blood flow in the medial temporal lobe (including the amygdala), of which greater bilateral amygdala blood flow decreases were associated with greater improvements in depressive symptoms (78). Additional gCBF reductions were observed in the temporal and parietal lobes. Resting state connectivity analyses in this sample produced evidence for increased connectivity

at post-treatment between cortical portions of the brain's default mode network (subgenual cingulate and precuneus; ventromedial prefrontal cortex and inferior parietal cortex), but decreased connectivity was observed between the parahippocampal gyri and the areas of the anterior medial and lateral frontopolar cortex. This latter finding is intriguing given that an exploratory analysis in this study found that greater parahippocampal gyri connectivity decreases were associated with greater degree of self-report peak or "mystical" experiences under the influence of psilocybin, which converges with prior work in healthy volunteers suggesting that parahippocampal disconnection from higher order cortical regions may, in part, mediate the subjective experience of "ego dissolution" (60). However, findings for increased connectivity within the default mode network (both seed and network-based) following psilocybin are counterintuitive given frequent findings for hyperconnectivity of the default mode network in the depressed state, which is typically associated with symptom facets such as rumination (79, 80). A recent re-analysis of resting state fMRI data from this open-label trial (81), also including new data from a randomized double-blind comparator of psilocybin and escitalopram (82), examined network modularity (a network-based measure of information flow across regions of the cortex, with higher modularity indicating less global information flow throughout the network)(83). Brain network modularity was significantly reduced 1 day following psilocybin in the open-label trial, and greater reductions were associated with greater improvements in depression symptoms from baseline to 6 months out (83). A similar decrease in network modularity in the psilocybin vs. escitalopram trial (this time examining the brain 3 weeks after a two doses of psilocybin) revealed a similar decrease for psilocybin but not escitalopram, though the change was not statistically different between the two arms. Magnitude of change was, however, also associated with reductions in depression symptoms from baseline to the post-treatment timepoint in the psilocybin arm but not the escitalopram arm. Additional analyses suggested that these effects might be most localizable to changes within the default mode network and between this network and other frontal cognitive networks. These findings, though not entirely convergent, do continue to home in on the default

mode network, measured at rest, as being a particularly salient marker of neurobiological changes following psilocybin with psychological support/therapy (PST) for MDD.

The examination of facial emotion processing changes in the open-label MDD trial (81) likewise produced counterintuitive findings for increased right amygdala activation to both fearful and happy faces one day post-treatment, of which right amygdala increases were associated with better clinical outcomes one week later (84). This is surprising for multiple reasons, including the observation that psilocybin attenuates amygdala activation to facial emotions in healthy individuals acutely (72) and at one week post-administration (76), but also because other pharmacological treatments for depression have produced evidence for a down-regulation of amygdala activity to negative emotional stimuli (85). There are several possible explanations, including the possibility that psilocybin's therapeutic effects operate via a qualitatively different mechanistic process from those of antidepressants, that amygdala activation to emotional faces may be an incomplete probe of therapeutic mechanisms, or that the time course of induced brain changes may vary across time from the immediate to the longer-term post-treatment phase. To the second point, a follow-up publication in this sample of depressed participants demonstrated that right amygdala connectivity during emotional (specifically fearful) face processing was altered post-psilocybin and was characterized by decreased connectivity with the ventromedial prefrontal cortex but increased connectivity with the occipital and parietal cortices, which suggests that increased amygdala activation co-occurs alongside an alteration in functional coherence with its typical cortical connectivity targets (86). A recent examination of functional brain changes in a patient population examined cognitive and neural flexibility 1 week following psilocybin with PST in patients with MDD (42). This sample, of which clinical findings had been previously reported (87), consisted of 24 individuals undergoing either immediate or delayed treatment with 20 mg/70kg and 30 mg/70kg of psilocybin in a dose-ascending order. Dynamic resting state functional connectivity of the anterior and posterior cingulate cortices was utilized as a measure of "neural flexibility", whereas cognitive flexibility was indexed with a behavioral task requiring set-

shifting for effective completion. Though cognitive flexibility was increased up to 4 weeks following psilocybin administration and dynamic functional connectivity between the anterior and posterior cingulate increased, the relationship between these measures suggested that greater neural flexibility increases were associated with lesser improvements in behavioral performance, which was interpreted to suggest a complex inverted-U relationship between neural flexibility and cognitive flexibility. These findings highlight the very challenging nature of attempting to elucidate therapeutic mechanisms of treatments with only a small subset of the various possible measures and outcomes that could be examined, also in relatively small samples. Ultimately, more studies are needed with repeated measurements over time both during and after psilocybin administration in healthy and patient populations to better address these questions and inform neurobiological understanding of therapeutic mechanisms.

The Structure and Delivery of Psilocybin with Psychological Support/Therapy (PST)

With a few notable exceptions (88-92), most research conducted examining psilocybin for therapeutic benefits has utilized psychological support and an educational framework delivered in the context of individual therapy with two therapeutic providers. The structure and delivery of the psychosocial component of this supportive intervention are explained in detail in prior publications (82, 93), and we briefly summarize that literature here. There are three phases of psilocybin treatment that are generally referred to as preparation, dosing (of the psychoactive substance), and integration or aftercare. Treatment is generally delivered in the context of at least one and usually two therapists for each participant during preparation, dosing, and integration phases. At least one of these therapists is the primary or lead therapist/monitor, while the other may either be a primary/lead therapist or monitor or an assistant therapist/monitor. Sometimes this distinction refers to the level of training/the highest degree of education attained or the degree of involvement in study procedures (with the lead/primary therapist often being a full-time, experienced licensed mental health provider and the assistant being a mental health trainee

and/or a part-time volunteer)(82). In other contexts, it may refer to the degree of responsibility or involvement of the therapist in the psychological support procedures (with the primary/lead therapist being present for all sessions and phases of therapy and the assistant being present during only a subset)(93). It is also sometimes emphasized that the therapist team include one member of each gender or two members of the same gender as the participant to facilitate feelings of safety and security. The therapists should be well-trained and knowledgeable of the effects of the study drug on an individual's state of consciousness as well as sensitive to the potential onset of difficult or challenging drug-induced experiences that might emerge in the course of a dosing session; possess a high degree of empathy, emotional intelligence, and the ability to form a supportive, trusting, and caring relationship with the study participant; and they should also be versed in methods of psychological support (e.g., breathing exercises, grounding techniques, offering of trust/reassurance) that can be utilized with the participant during a dosing session to help the participant manage any difficult or challenging experiences that may arise (93). The physical setting in which the therapeutic sessions take place is designed with a careful eye toward aesthetics and comfort, with the primary intent being to facilitate feelings of safety in the participant and to ensure actual safety when the participant is under the effects of a drug. Settings typically include a "living room-like" environment, complete with artwork, couches, reclining beds, armchairs, artwork, sculptures, and ambient lighting (93). The rooms are generally designed to be quiet, private, removed from a lot of foot traffic, and with a nearby or adjoining private restroom for use by the participant during dosing sessions.

The first phase of treatment involves preparation for the subsequent dosing session(s) in the form of one or several meetings with the therapist/co-therapist team. During these meetings, the primary emphasis is on informed consent and psychoeducation regarding the characteristic mind-altering effects of psilocybin and establishing therapeutic rapport and a mutual sense of trust between therapist(s) and the participant. This process typically occurs over the course of 3 to 8 hours over 1 to 4 weeks in one or more meetings (81, 82, 87). During these sessions, the

therapist(s) and participant typically discuss the participant's life history and current life status, including childhood and formative experiences, current life circumstances, significant relationships and family members, current living situation, the experience of living with the psychiatric diagnosis of interest, manifestation of symptoms and impact on functioning, etc. The participant is encouraged and reinforced for open and honest communication, thereby facilitating comfort with the therapist(s), and laying the groundwork for a relationship of unconditional acceptance and positive regard that is highly important for facilitating a sense of safety and trust while under the influence of psilocybin. The participant and therapist(s) will also discuss study logistics and appointments, and the therapist(s) will then provide the participant with psychoeducation on the typical and possible subjective effects of psilocybin. Particular attention is paid to striking a balance between extensive disclosure and preparation for what might occur during the dosing session vs. priming the participant to expect certain types of characteristic experiences during the dosing session (93). Participants are also instructed on cultivating willingness and openness to experiencing whatever arises for them during the dosing session, with the primary emphasis being on moving towards and through rather than away from unpleasant feelings/thoughts/sensations. The predominant emphasis is on "surrender" to experiences that are uncomfortable or frightening and "acceptance" of uncomfortable sensations/emotions by reminding the participant that the effects of the drug are transient and temporary and that the drug itself is quite safe with an extensive history of use by humans, and that no matter how unfamiliar the state of consciousness engendered by the drug, the participant will return to a normal state of consciousness within a matter of hours (82, 93). The role of music and eyeshades are discussed, often with the option for the participant to practice with the headphones, eyeshades, and the setup to be utilized during the dosing sessions. It is prudent to emphasize here that one of the factors that appear to be ubiquitous across modern therapeutic investigations of psilocybin is the use of pre-selected music to be delivered during the drug experience, often through headphones and with the addition of eyeshades to encourage

individuals to focus their attention inward. This music is often classical or instrumental/ambient in nature (82, 87) and frequently selected with the consideration of minimal language content of the participant's capacity for comprehension (which may interfere with the participant's experience) and with a varying range of intensity/tempo to support both calm/introverted awareness and more energetic emotionally-evocative states of affect, often sequenced in such a way as to coincide with the onset, peak, and receding of subjective drug effects (94). Recent research has demonstrated that psychedelics both enhance the emotional response to music (95) and can likewise facilitate the generation of personally meaningful and therapeutically-useful emotion and visual imagery during the administration of a psychedelic (96), which provides empirical support for clinical and anecdotal observations that music is one critical facet of the therapeutic setting that may facilitate the most advantageous subjective drug experience.

Dosing sessions typically commence in the morning to allow for the prolonged duration of psilocybin's action that necessitates sessions lasting 4 to 6 hours. A medical doctor, if not physically present in the room as one of the therapists, is often kept on-call in case of any type of medical emergency. After the drug is administered (typically orally), participants are often encouraged to lie down or recline in a comfortable position, place headphones and/or eyeshades, and focus their attention inward. At the same time, pre-selected music is played at a comfortable volume. If there are two therapists, both are typically present during the entirety of the dosing sessions, except for brief room exits for biological self-care. Therapists will often sit on either side of the participant while reclined. Other models utilize a lead therapist that is present in the room for the majority of the session while a "floating" therapist will step in, as needed, to relieve the lead therapist for breaks. As the effects of psilocybin begin to manifest, the participant may signal to the therapist(s) when they require or desire support, sometimes delivered in the form of physical contact (e.g., handholding). Conversation during the early and middle phases of the dosing session is often kept to a minimum, as the participant is typically encouraged to focus their attention inward as much as possible (82). If the participant begins to experience an acute anxiety

or panic reaction, the therapist(s) will typically attempt to reassure the participant calmly that they are safe, and all is well while sometimes encouraging them to “accept” or “surrender to” the uncomfortable experience. Physical touch is often utilized as a powerful form of reassurance, i.e., handholding, placing a hand on the shoulder, etc. Note that touch in this context is always pre-negotiated with the participant before the dosing session and is often prefaced with a question (“Would you like me to hold your hand?”) before its initiation. Reassurance in the verbal or physical modality is often sufficient to calm acute anxiety or panic reactions. Still, pharmacological aids are typically kept on hand (though rarely ever utilized in modern reported research trials) in the form of fast-acting oral benzodiazepines and oral atypical antipsychotic agents that antagonize the 5-HT_{2A} receptor (e.g., risperidone). As the drug effect begins to abate, the participant may be more talkative and engage in more conversation with the therapist(s) as their typical state of consciousness returns. However, in-depth analysis of the drug experience by the participant and/or therapist(s) is typically not utilized during this phase, and the participant is encouraged to refrain from heavy introspection regarding the meaning of various phenomena and is instead encouraged to remain open to the experience as it continues to unfold while subsequent integration sessions will be devoted to more in-depth analysis (93). After the effects of psilocybin have abated, the participant is either typically released into the care of a relative or close friend (who will drive them home from the appointment), or the participant is placed into an acute aftercare setting such as a monitored overnight stay at a nearby hospital or treatment facility. In either case, at this stage, it is considered critical to monitor for any adverse post-acute effects that may require immediate medical or clinical attention. However, modern clinical trials have not reported adverse effects in the immediate post-acute phase requiring immediate medical intervention.

Integration sessions typically commence the following day and may occur with one or both members of the therapist team. The initial session often involves a safety check-in to assess for the onset of any adverse events or uncomfortable side effects and an open discussion regarding

the participant's subjective experience of the drug effects the day prior. The participant may be encouraged to reflect and elaborate on the novel thoughts, feelings, and experiences that occurred during their dosing sessions, and the therapist(s) may offer additional commentary, insights, or questions that aid the participant in coming to a subjective sense of insight or revelation regarding the drug-induced experiences (93). Visualization exercises have also been offered as a way to help the participant reconnect to emotions they accessed while under the influence of the psilocybin (82). Subsequent integration sessions may be offered on separate days in the following weeks, frequently with a similar emphasis on safety assessment, providing support and maintaining therapeutic rapport, discussion of evolving insight and understanding regarding the drug experience, and supporting the participant in therapeutically relevant goals about maintaining improvements or enacting positive lifestyle changes. Depending on the study protocol, integration sessions may be followed by one or more additional dosing sessions, each of which may be followed by additional integration sessions. It is interesting to note that, of all the phases of psilocybin with PST or psychedelic-assisted therapies, the integration or aftercare phase is the least well-codified in the current scientific literature regarding guiding premises, goals, and techniques or best practices. Whereas preparation and dosing are well-described in existing seminal publications (82, 93), the conduction of the integration or debriefing phase is described in less detail and more general, non-specific terms. This is notable as the integration and aftercare phase may be the most critical period during which deliberate psychological intervention is most critical to maintaining, sustaining, or enhancing the therapeutic effects that may have begun to manifest in the day/days following the dosing session. Additional research and documentation are needed to better inform the conduction and delivery of psychological support during this period of post-acute neurobiological and psychological change for maximal therapeutic benefit.

Supplemental References

1. Dinis-Oliveira RJ. Metabolism of psilocybin and psilocin: clinical and forensic toxicological relevance. Drug Metabolism Reviews. 2017;49:84-91.
2. Brown RT, Nicholas CR, Cozzi NV, Gassman MC, Cooper KM, Muller D, Thomas CD, Hetzel SJ, Henriquez KM, Ribaudo AS, Hutson PR. Pharmacokinetics of Escalating Doses of Oral Psilocybin in Healthy Adults. Clin Pharmacokinet. 2017;56:1543-1554.
3. Halberstadt AL, Geyer MA. Multiple receptors contribute to the behavioral effects of indoleamine hallucinogens. Neuropharmacology. 2011;61:364-381.
4. Vollenweider FX, Vollenweider-Scherpenhuyzen MF, Bäbler A, Vogel H, Hell D. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport. 1998;9:3897-3902.
5. Kometer M, Schmidt A, Bachmann R, Studerus E, Seifritz E, Vollenweider FX. Psilocybin biases facial recognition, goal-directed behavior, and mood state toward positive relative to negative emotions through different serotonergic subreceptors. Biol Psychiatry. 2012;72:898-906.
6. Quednow BB, Kometer M, Geyer MA, Vollenweider FX. Psilocybin-induced deficits in automatic and controlled inhibition are attenuated by ketanserin in healthy human volunteers. Neuropsychopharmacology. 2012;37:630-640.
7. Kometer M, Schmidt A, Jäncke L, Vollenweider FX. Activation of serotonin 2A receptors underlies the psilocybin-induced effects on α oscillations, N170 visual-evoked potentials, and visual hallucinations. J Neurosci. 2013;33:10544-10551.
8. DuPre A, Teitler M: Ketanserin. in xPharm: The Comprehensive Pharmacology Reference. Edited by Enna SJ, Bylund DB. New York, Elsevier; 2007. pp. 1-16.
9. Darchen F, Scherman D, Laduron PM, Henry JP. Ketanserin binds to the monoamine transporter of chromaffin granules and of synaptic vesicles. Mol Pharmacol. 1988;33:672-677.
10. Carter OL, Burr DC, Pettigrew JD, Wallis GM, Hasler F, Vollenweider FX. Using psilocybin to investigate the relationship between attention, working memory, and the serotonin 1A and 2A receptors. Journal of cognitive neuroscience. 2005;17:1497-1508.
11. Carter OL, Hasler F, Pettigrew JD, Wallis GM, Liu GB, Vollenweider FX. Psilocybin links binocular rivalry switch rate to attention and subjective arousal levels in humans. Psychopharmacology (Berl). 2007;195:415-424.
12. Madsen MK, Fisher PM, Burmester D, Dyssegaard A, Stenbæk DS, Kristiansen S, Johansen SS, Lehel S, Linnet K, Svarer C, Erritzoe D, Ozenne B, Knudsen GM. Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology. 2019;44:1328-1334.
13. Madsen MK, Knudsen GM. Plasma psilocin critically determines behavioral and neurobiological effects of psilocybin. Neuropsychopharmacology. 2021;46:257-258.
14. González-Maeso J, Weisstaub NV, Zhou M, Chan P, Ivic L, Ang R, Lira A, Bradley-Moore M, Ge Y, Zhou Q, Sealfon SC, Gingrich JA. Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. Neuron. 2007;53:439-452.
15. McClure-Begley TD, Roth BL. The promises and perils of psychedelic pharmacology for psychiatry. Nature Reviews Drug Discovery. 2022;21:463-473.
16. Holze F, Ley L, Müller F, Becker AM, Straumann I, Vizeli P, Kuehne SS, Roder MA, Duthaler U, Kolaczynska KE, Varghese N, Eckert A, Liechti ME. Direct comparison of the acute effects of lysergic acid diethylamide and psilocybin in a double-blind placebo-controlled study in healthy subjects. Neuropsychopharmacology. 2022.
17. Gouzoulis-Mayfrank E, Thelen B, Habermeyer E, Kunert HJ, Kovar KA, Lindenblatt H, Hermle L, Spitzer M, Sass H. Psychopathological, neuroendocrine and autonomic effects of 3,4-

methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental double-blind placebo-controlled study. Psychopharmacology (Berl). 1999;142:41-50.
18. Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. Psychopharmacology (Berl). 2004;172:145-156.
19. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl). 2006;187:268-283; discussion 284-292.
20. Griffiths R, Richards W, Johnson M, McCann U, Jesse R. Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. Journal of psychopharmacology (Oxford, England). 2008;22:621-632.
21. Griffiths RR, Johnson MW, Richards WA, Richards BD, McCann U, Jesse R. Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology (Berl). 2011;218:649-665.
22. MacLean KA, Johnson MW, Griffiths RR. Mystical experiences occasioned by the hallucinogen psilocybin lead to increases in the personality domain of openness. Journal of psychopharmacology (Oxford, England). 2011;25:1453-1461.
23. Dittrich A. The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. Pharmacopsychiatry. 1998;31 Suppl 2:80-84.
24. Studerus E, Gamma A, Vollenweider FX. Psychometric Evaluation of the Altered States of Consciousness Rating Scale (OAV). PLOS ONE. 2010;5:e12412.
25. Dittrich A, Lamparter D, Maurer M: A short introduction. Switzerland, PSIN PLUS; 2010.
26. Strassman RJ, Qualls CR. Dose-response study of N,N-dimethyltryptamine in humans. I. Neuroendocrine, autonomic, and cardiovascular effects. Archives of general psychiatry. 1994;51:85-97.
27. Strassman RJ, Qualls CR, Uhlenhuth EH, Kellner R. Dose-Response Study of N,N-Dimethyltryptamine in Humans: II. Subjective Effects and Preliminary Results of a New Rating Scale. Archives of general psychiatry. 1994;51:98-108.
28. Riba J, Rodríguez-Fornells A, Strassman RJ, Barbanoj MJ. Psychometric assessment of the Hallucinogen Rating Scale. Drug and alcohol dependence. 2001;62:215-223.
29. Pahnke WN: Drugs and Mysticism: An Analysis of the Relationship Between Psychedelic Drugs and the Mystical Consciousness. Cambridge, MA, Harvard University Press; 1963.
30. Stace WT. Mysticism and philosophy. 1960.
31. Barrett FS, Johnson MW, Griffiths RR. Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. Journal of Psychopharmacology. 2015;29:1182-1190.
32. Nicholas CR, Henriquez KM, Gassman MC, Cooper KM, Muller D, Hetzel S, Brown RT, Cozzi NV, Thomas C, Hutson PR. High dose psilocybin is associated with positive subjective effects in healthy volunteers. Journal of psychopharmacology (Oxford, England). 2018;32:770-778.
33. Carbonaro TM, Johnson MW, Hurwitz E, Griffiths RR. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: similarities and differences in subjective experiences. Psychopharmacology (Berl). 2018;235:521-534.
34. Gouzoulis-Mayfrank E, Heekeren K, Thelen B, Lindenblatt H, Kovar KA, Sass H, Geyer MA. Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. Behav Pharmacol. 1998;9:561-566.

35. Gouzoulis-Mayfrank E, Thelen B, Maier S, Heekeren K, Kovar KA, Sass H, Spitzer M. Effects of the hallucinogen psilocybin on covert orienting of visual attention in humans. Neuropsychobiology. 2002;45:205-212.
36. Umbricht D, Vollenweider FX, Schmid L, Grübel C, Skrabo A, Huber T, Koller R. Effects of the 5-HT2A agonist psilocybin on mismatch negativity generation and AX-continuous performance task: implications for the neuropharmacology of cognitive deficits in schizophrenia. Neuropsychopharmacology. 2003;28:170-181.
37. Carter OL, Pettigrew JD, Burr DC, Alais D, Hasler F, Vollenweider FX. Psilocybin impairs high-level but not low-level motion perception. Neuroreport. 2004;15:1947-1951.
38. Vollenweider FX, Csomor PA, Knappe B, Geyer MA, Quednow BB. The effects of the preferential 5-HT2A agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. Neuropsychopharmacology. 2007;32:1876-1887.
39. Carter OL, Pettigrew JD, Hasler F, Wallis GM, Liu GB, Hell D, Vollenweider FX. Modulating the rate and rhythmicity of perceptual rivalry alternations with the mixed 5-HT2A and 5-HT1A agonist psilocybin. Neuropsychopharmacology. 2005;30:1154-1162.
40. Barrett FS, Carbonaro TM, Hurwitz E, Johnson MW, Griffiths RR. Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: effects on cognition. Psychopharmacology (Berl). 2018;235:2915-2927.
41. Mason NL, Kuypers KPC, Reckweg JT, Müller F, Tse DHY, Da Rios B, Toennes SW, Stiers P, Feilding A, Ramaekers JG. Spontaneous and deliberate creative cognition during and after psilocybin exposure. Translational Psychiatry. 2021;11:209.
42. Doss MK, Považan M, Rosenberg MD, Sepeda ND, Davis AK, Finan PH, Smith GS, Pekar JJ, Barker PB, Griffiths RR, Barrett FS. Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. Translational Psychiatry. 2021;11:574.
43. Rucker JJ, Marwood L, Ajantaival R-LJ, Bird C, Eriksson H, Harrison J, Lennard-Jones M, Mistry S, Saldarini F, Stansfield S, Tai SJ, Williams S, Weston N, Malievskaia E, Young AH. The effects of psilocybin on cognitive and emotional functions in healthy participants: Results from a phase 1, randomised, placebo-controlled trial involving simultaneous psilocybin administration and preparation. Journal of Psychopharmacology. 2022:02698811211064720.
44. Wittmann M, Carter O, Hasler F, Cahn BR, Grimberg U, Spring P, Hell D, Flohr H, Vollenweider FX. Effects of psilocybin on time perception and temporal control of behaviour in humans. Journal of psychopharmacology (Oxford, England). 2007;21:50-64.
45. Wackermann J, Wittmann M, Hasler F, Vollenweider FX. Effects of varied doses of psilocybin on time interval reproduction in human subjects. Neuroscience letters. 2008;435:51-55.
46. Dziobek I, Rogers K, Fleck S, Bahnemann M, Heekeren HR, Wolf OT, Convit A. Dissociation of cognitive and emotional empathy in adults with Asperger syndrome using the Multifaceted Empathy Test (MET). J Autism Dev Disord. 2008;38:464-473.
47. Pokorny T, Preller KH, Kometer M, Dziobek I, Vollenweider FX. Effect of Psilocybin on Empathy and Moral Decision-Making. Int J Neuropsychopharmacol. 2017;20:747-757.
48. Gabay AS, Carhart-Harris RL, Mazibuko N, Kempton MJ, Morrison PD, Nutt DJ, Mehta MA. Psilocybin and MDMA reduce costly punishment in the Ultimatum Game. Sci Rep. 2018;8:8236.
49. Vollenweider FX, Leenders KL, Scharfetter C, Maguire P, Stadelmann O, Angst J. Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. Neuropsychopharmacology. 1997;16:357-372.
50. Gouzoulis-Mayfrank E, Schreckenberger M, Sabri O, Arning C, Thelen B, Spitzer M, Kovar KA, Hermle L, Büll U, Sass H. Neurometabolic effects of psilocybin, 3,4-methylenedioxyethylamphetamine (MDE) and d-methamphetamine in healthy volunteers. A

double-blind, placebo-controlled PET study with [18F]FDG. Neuropsychopharmacology. 1999;20:565-581.
51. Carhart-Harris RL, Erritzoe D, Williams T, Stone JM, Reed LJ, Colasanti A, Tyacke RJ, Leech R, Malizia AL, Murphy K, Hobden P, Evans J, Feilding A, Wise RG, Nutt DJ. Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A. 2012;109:2138-2143.
52. Lewis CR, Preller KH, Kraehenmann R, Michels L, Staempfli P, Vollenweider FX. Two dose investigation of the 5-HT-agonist psilocybin on relative and global cerebral blood flow. Neuroimage. 2017;159:70-78.
53. Greicius MD, Krasnow B, Reiss AL, Menon V. Functional connectivity in the resting brain: a network analysis of the default mode hypothesis. Proc Natl Acad Sci U S A. 2003;100:253-258.
54. Carhart-Harris RL, Leech R, Erritzoe D, Williams TM, Stone JM, Evans J, Sharp DJ, Feilding A, Wise RG, Nutt DJ. Functional connectivity measures after psilocybin inform a novel hypothesis of early psychosis. Schizophr Bull. 2013;39:1343-1351.
55. Vollenweider FX, Preller KH. Psychedelic drugs: neurobiology and potential for treatment of psychiatric disorders. Nature Reviews Neuroscience. 2020;21:611-624.
56. Roseman L, Leech R, Feilding A, Nutt DJ, Carhart-Harris RL. The effects of psilocybin and MDMA on between-network resting state functional connectivity in healthy volunteers. Front Hum Neurosci. 2014;8:204.
57. Madsen MK, Stenbæk DS, Arvidsson A, Armand S, Marstrand-Joergensen MR, Johansen SS, Linnet K, Ozenne B, Knudsen GM, Fisher PM. Psilocybin-induced changes in brain network integrity and segregation correlate with plasma psilocin level and psychedelic experience. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2021;50:121-132.
58. Palhano-Fontes F, Andrade KC, Tofoli LF, Santos AC, Crippa JA, Hallak JE, Ribeiro S, de Araujo DB. The psychedelic state induced by ayahuasca modulates the activity and connectivity of the default mode network. PLoS One. 2015;10:e0118143.
59. Varley TF, Carhart-Harris R, Roseman L, Menon DK, Stamatakis EA. Serotonergic psychedelics LSD & psilocybin increase the fractal dimension of cortical brain activity in spatial and temporal domains. Neuroimage. 2020;220:117049.
60. Lebedev AV, Lövdén M, Rosenthal G, Feilding A, Nutt DJ, Carhart-Harris RL. Finding the self by losing the self: Neural correlates of ego-dissolution under psilocybin. Hum Brain Mapp. 2015;36:3137-3153.
61. Uddin LQ: Chapter 3 - Functions of the Salience Network. in Salience Network of the Human Brain. Edited by Uddin LQ. San Diego, Academic Press; 2017. pp. 11-16.
62. Mathur B. The claustrum in review. Frontiers in Systems Neuroscience. 2014;8.
63. Krimmel SR, White MG, Panicker MH, Barrett FS, Mathur BN, Seminowicz DA. Resting state functional connectivity and cognitive task-related activation of the human claustrum. NeuroImage. 2019;196:59-67.
64. Zhang G, Stackman RW, Jr. The role of serotonin 5-HT2A receptors in memory and cognition. Frontiers in pharmacology. 2015;6:225-225.
65. Barrett FS, Krimmel SR, Griffiths RR, Seminowicz DA, Mathur BN. Psilocybin acutely alters the functional connectivity of the claustrum with brain networks that support perception, memory, and attention. Neuroimage. 2020;218:116980.
66. Carhart-Harris RL, Leech R, Williams TM, Erritzoe D, Abbasi N, Bargiotas T, Hobden P, Sharp DJ, Evans J, Feilding A, Wise RG, Nutt DJ. Implications for psychedelic-assisted psychotherapy: functional magnetic resonance imaging study with psilocybin. The British journal of psychiatry : the journal of mental science. 2012;200:238-244.
67. Healy CJ. The acute effects of classic psychedelics on memory in humans. Psychopharmacology (Berl). 2021.

68. Hamilton JP, Etkin A, Furman DJ, Lemus MG, Johnson RF, Gotlib IH. Functional neuroimaging of major depressive disorder: a meta-analysis and new integration of base line activation and neural response data. Am J Psychiatry. 2012;169:693-703.
69. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am J Psychiatry. 2007;164:1476-1488.
70. Feinstein JS, Adolphs R, Damasio A, Tranel D. The human amygdala and the induction and experience of fear. Curr Biol. 2011;21:34-38.
71. Costafreda SG, Brammer MJ, David AS, Fu CH. Predictors of amygdala activation during the processing of emotional stimuli: a meta-analysis of 385 PET and fMRI studies. Brain Res Rev. 2008;58:57-70.
72. Kraehenmann R, Preller KH, Scheidegger M, Pokorny T, Bosch OG, Seifritz E, Vollenweider FX. Psilocybin-Induced Decrease in Amygdala Reactivity Correlates with Enhanced Positive Mood in Healthy Volunteers. Biol Psychiatry. 2015;78:572-581.
73. Bernasconi F, Schmidt A, Pokorny T, Kometer M, Seifritz E, Vollenweider FX. Spatiotemporal brain dynamics of emotional face processing modulations induced by the serotonin 1A/2A receptor agonist psilocybin. Cerebral cortex (New York, NY : 1991). 2014;24:3221-3231.
74. Grimm O, Kraehenmann R, Preller KH, Seifritz E, Vollenweider FX. Psilocybin modulates functional connectivity of the amygdala during emotional face discrimination. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2018;28:691-700.
75. Preller KH, Pokorny T, Hock A, Kraehenmann R, Stämpfli P, Seifritz E, Scheidegger M, Vollenweider FX. Effects of serotonin 2A/1A receptor stimulation on social exclusion processing. Proc Natl Acad Sci U S A. 2016;113:5119-5124.
76. Barrett FS, Doss MK, Sepeda ND, Pekar JJ, Griffiths RR. Emotions and brain function are altered up to one month after a single high dose of psilocybin. Sci Rep. 2020;10:2214.
77. McCulloch DE, Madsen MK, Stenbæk DS, Kristiansen S, Ozenne B, Jensen PS, Knudsen GM, Fisher PM. Lasting effects of a single psilocybin dose on resting-state functional connectivity in healthy individuals. Journal of psychopharmacology (Oxford, England). 2021:2698811211026454.
78. Carhart-Harris RL, Roseman L, Bolstridge M, Demetriou L, Pannekoek JN, Wall MB, Tanner M, Kaelen M, McGonigle J, Murphy K, Leech R, Curran HV, Nutt DJ. Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Scientific Reports. 2017;7:13187.
79. Hamilton JP, Farmer M, Fogelman P, Gotlib IH. Depressive Rumination, the Default-Mode Network, and the Dark Matter of Clinical Neuroscience. Biol Psychiatry. 2015;78:224-230.
80. Kaiser RH, Andrews-Hanna JR, Wager TD, Pizzagalli DA. Large-Scale Network Dysfunction in Major Depressive Disorder: A Meta-analysis of Resting-State Functional Connectivity. JAMA Psychiatry. 2015;72:603-611.
81. Carhart-Harris RL, Bolstridge M, Rucker J, Day CM, Erritzoe D, Kaelen M, Bloomfield M, Rickard JA, Forbes B, Feilding A, Taylor D, Pilling S, Curran VH, Nutt DJ. Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. The lancet Psychiatry. 2016;3:619-627.
82. Carhart-Harris R, Giribaldi B, Watts R, Baker-Jones M, Murphy-Beiner A, Murphy R, Martell J, Blemings A, Erritzoe D, Nutt DJ. Trial of Psilocybin versus Escitalopram for Depression. New England Journal of Medicine. 2021;384:1402-1411.
83. Daws RE, Timmermann C, Giribaldi B, Sexton JD, Wall MB, Erritzoe D, Roseman L, Nutt D, Carhart-Harris R. Increased global integration in the brain after psilocybin therapy for depression. Nat Med. 2022;28:844-851.

84. Roseman L, Demetriou L, Wall MB, Nutt DJ, Carhart-Harris RL. Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. Neuropharmacology. 2018;142:263-269.
85. Ma Y. Neuropsychological mechanism underlying antidepressant effect: a systematic meta-analysis. Mol Psychiatry. 2015;20:311-319.
86. Mertens LJ, Wall MB, Roseman L, Demetriou L, Nutt DJ, Carhart-Harris RL. Therapeutic mechanisms of psilocybin: Changes in amygdala and prefrontal functional connectivity during emotional processing after psilocybin for treatment-resistant depression. Journal of psychopharmacology (Oxford, England). 2020;34:167-180.
87. Davis AK, Barrett FS, May DG, Cosimano MP, Sepeda ND, Johnson MW, Finan PH, Griffiths RR. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. JAMA Psychiatry. 2021;78:481-489.
88. Johnson MW, Garcia-Romeu A, Cosimano MP, Griffiths RR. Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. Journal of psychopharmacology (Oxford, England). 2014;28:983-992.
89. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa PC, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. Journal of psychopharmacology (Oxford, England). 2015;29:289-299.
90. Anderson BT, Danforth A, Daroff PR, Stauffer C, Ekman E, Agin-Liebes G, Trope A, Boden MT, Dilley PJ, Mitchell J, Woolley J. Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. EClinicalMedicine. 2020;27:100538.
91. Shnayder S, Ameli R, Sinaii N, Berger A, Agrawal M. Psilocybin-assisted therapy improves psycho-social-spiritual well-being in cancer patients. J Affect Disord. 2023;323:592-597.
92. Lewis BR, Garland EL, Byrne K, Durns T, Hendrick J, Beck A, Thielking P. HOPE: A Pilot Study of Psilocybin Enhanced Group Psychotherapy in Patients With Cancer. J Pain Symptom Manage. 2023;66:258-269.
93. Johnson M, Richards W, Griffiths R. Human hallucinogen research: guidelines for safety. Journal of psychopharmacology (Oxford, England). 2008;22:603-620.
94. Barrett FS, Robbins H, Smooke D, Brown JL, Griffiths RR. Qualitative and Quantitative Features of Music Reported to Support Peak Mystical Experiences during Psychedelic Therapy Sessions. Front Psychol. 2017;8:1238.
95. Kaelen M, Barrett FS, Roseman L, Lorenz R, Family N, Bolstridge M, Curran HV, Feilding A, Nutt DJ, Carhart-Harris RL. LSD enhances the emotional response to music. Psychopharmacology (Berl). 2015;232:3607-3614.
96. Kaelen M, Giribaldi B, Raine J, Evans L, Timmerman C, Rodriguez N, Roseman L, Feilding A, Nutt D, Carhart-Harris R. The hidden therapist: evidence for a central role of music in psychedelic therapy. Psychopharmacology (Berl). 2018;235:505-519.

TABLE S1. Inclusion/Exclusion Criteria, Outcomes, and Adverse Events for Psilocybin Studies in Obsessive-Compulsive and Related Disorders

Publication(s)	Key Inclusion Criteria	Key Exclusion Criteria	Primary Outcomes	Secondary Outcomes	Adverse Events
Moreno et al.,2006	•SCID-IV OCD diagnosis •Prior failure of at least 1 SSRI	•Comorbid psychiatric conditions •Personal or family history of psychosis •Not having at least 1 prior positive psychedelic experience •Current medications	•YBOCS •VAS for overall OCD severity	•HRS	•N=1 transient high blood pressure •N=2 discontinued after first dosing due to hospital stay afterwards
Schneier et al., 2023	•Ages 18-55 •Principal diagnosis of non-delusional BDD for >6 months •Moderate severity BDD (score of 24 or higher on BDD-YBOCS and score on CGI severity scale of 4 or more) •History of non-response to or intolerance of a prior trial of a selective serotonin reuptake inhibitor, serotonin-norepinephrine reuptake inhibitor, or clomipramine at a dose equivalent to 20mg or more of fluoxetine for 2 months or more	•Current major depressive disorder diagnosis of greater than moderate severity •Current significant suicidality or attempt in the past year •Current or past psychotic disorder, bipolar disorder, borderline personality disorder, or dissociative identity disorder •Current or past 3-month substance-use disorder •Serotonergic medication within 2 weeks (6 weeks for fluoxetine) •Significant medical illness •Pregnant or breast-feeding female, or female unwilling to use contraception •Current cognitive-behavioral therapy	•BDD-YBOCS	•CGI Change scale •17-item HAM-D •BABS •DCQ •PANAS •SDS •PIS •C-SSRS	•Fatigue (N=5) •Headache (N=3) •Nausea (N=2) •Somnolence (N=1) •Lightheadedness (N=1) •Insomnia (N=1) •Spaciness (N=1) •N=1 reported several possible drug-related AEs persisting beyond the first week: low libido, brief episodes of emotion and mood disturbance (tearfulness, sadness), four episodes of visual hallucinations

BABS = Brown Assessment of Beliefs Scale; BDD-YBOCS = Yale-Brown Obsessive Compulsive Scale modified for body dysmorphic disorder; CGI = Clinical Global Impression; C-SSRS = Columbia Suicide Severity Rating Scale; DCQ = Dysmorphic Concerns Questionnaire; HAM-D = Hamilton Depression Rating Scale; HRS = Hallucinogen Rating Scale; PANAS = Positive and Negative Affect Scale; PIS = Psychological Insight Scale; SCID-IV = Structured Clinical Interview for DSM-IV Diagnosis; SDS = Sheehan Disability Scale; SSRI = selective serotonin reuptake inhibitor; YBOCS = Yale Brown Obsessive Compulsive Scale;

TABLE S2. Inclusion/Exclusion Criteria, Outcomes, and Adverse Events for Psilocybin Studies in Anxiety and Depression Associated with Life-Threatening Cancer

Publication(s)	Key Inclusion Criteria	Key Exclusion Criteria	Primary Outcomes	Secondary Outcomes	Adverse Events
Grob et al., 2011	•Advanced-stage cancer •DSM-IV diagnosis of acute stress d/o, GAD, anxiety d/o due to cancer, or adjustment d/o with anxiety	•Neurologic issues •Untreated high blood pressure •Personal or family history of psychosis or bipolar d/o •Anxiety or mood d/o with onset within 1 year prior to cancer diagnosis •Current medications	•BDI •POMS •STAI	•5D-ASC •BPRS	•Minor increases in blood pressure and heart rate •No serious AEs
Griffiths et al., 2016	•Age 21 to 80 with potentially life-threatening cancer diagnosis •DSM-IV diagnosis with anxiety and/or mood symptoms precipitated or exacerbated by cancer diagnosis	•CNS disease •Hepatic dysfunction •Cardiac conditions •High blood pressure •Epilepsy or h/o seizures. •Renal insufficiency •Type I diabetes •Pregnancy •Certain meds • Suicidal ideation •Current or past history of psychosis or bipolar d/o •Current alcohol or drug dependence or in past 5 years •1st or 2nd degree relative with psychosis or bipolar d/o •Current dissociative d/o, eating d/o, or other psych conditions interfering with rapport building or safe exposure to psilocybin.	•GRID-HAM-D •SIGH-A Response defined as ≥ 50% reduction from baseline. Remission defined as score ≤ 7.	•HADS •BDI	•Increases in blood pressure (34% and 17% in high and low doses) •Nausea or vomiting (15% in high doses), •Physical discomfort (21% and 8% in high and low doses, •Psych distress (32% and 12% in high and low doses), •Anxiety (26% and 15% in high and low doses), •Paranoid ideation (N=1 in high dose session). •Headache (N=1 after dosing; N=11 the following day)
Ross et al., 2016; Agin-Liebes et al. 2020	•Age 18 to 76 •Life expectancy of at least one year •DSM-IV diagnosis of acute stress d/o, GAD, anxiety d/o due to cancer, or adjustment d/o with anxiety or mixed anxiety and depression.	•HADS total score < 8 •Medical conditions that would interfere with study participation •Personal or family h/o psychosis or bipolar d/o •Current substance use disorder	•HADS •BDI •STAI Response defined as ≥ 50% reduction from baseline. Depression remission defined as response and post-treatment HADS-D score ≤ 7 or BDI ≤ 12.	•DEM •HAI •DAS •DTS •WHO-Qol •FACIT-SWB •MEQ-30 •PEQ	•Elevations in blood pressure and heart rate (76%) •Headaches/migraines (28%) •Nausea (14%); •Anxiety (17%) •Transient psychotic-like symptoms (7%)

Lewis et al., 2023	•Male or female, age > 25, diagnosed with cancer and currently undergoing treatment or completed treatment within < 26 weeks of study registration. •Life expectancy > 3 months. •Not taking regularly scheduled medications to treat depression and/or anxiety, including benzodiazepines, for at least 4 weeks prior to study initiation •PHQ-9 > or = 10 within 28 days of registration. • ECOG Performance Status > 2. •Adequate liver function •For female subjects of pregnancy potential: Not pregnant and agree to use contraception •For male subjects: agree to condom use during intercourse for 24 hours post psilocybin dose.	•Psychiatric med use within 4 weeks of study initiation • Personal or family history of psychosis or bipolar d/o •Severe depression requiring immediate standard of care treatment •Past month suicidal ideation •Cancer with CNS involvement •Current or recent past history (2 years) of substance use disorder diagnosis •Employment as Emergency Department house staff •Physical conditions/illnesses contraindicated for psilocybin	•Feasibility (rates of recruitment and retention) •Safety (adverse events and suicidal ideation as measured by the CSSRS •HAM-D	•FACIT-SWB •DTS	•Nausea (N=5) •Hypertension (N=1) •Hypotension (N=1) •Headache (N=3) •Ventricular tachycardia (N=1) •Vomiting (N=1)
Agrawal et al., 2023; Shnayder et al., 2023	•Age 18 or older •MDD single episode or recurrent without psychotic features •HAM-D score of 18 or more at baseline •Malignant neoplasm	•Current or past history of psychotic, bipolar, or borderline personality disorder •Significant suicide risk	•MADRS •NIH-HEALS	•Assessed but not reported as outcomes: HAM-A, CSSRS, EQ-5D-5L, SDS	•Headache (N=24) •Nausea (N=12) •Tearfulness (N=8) •Anxiety (N=7) •Euphoria (N=7) •Fatigue (N=7) •Mild impairment in psychomotor functioning (N=3)

5D-ASC = Five Dimensional Altered States of Consciousness Scale; Aes = adverse events; BDI = Beck Depression Inventory; BPRS = Brief Psychiatric Rating Scale; CSSRS = Columbia Suicide Severity Rating Scale; d/o = disorder; DAS = Death Anxiety Scale; DEM = Demoralization Scale; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders 4th Edition; DTS = Death Transcendence Scale; EQ-5D-5L = Euro Quality of Life 5 Dimensions; FACIT-SWB = Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being; GAD = generalized anxiety disorder; GRID-HAM-D = Structured Clinical Interview Assessment for the Hamilton Depression Rating Scale; HADS = Hospital Anxiety and Depression Scale; HAI = Hopelessness Assessment and Illness Scale; h/o = history of; HAM-D: Hamilton Depression Rating Scale; MEQ-30 = 30-item Mystical Experience Questionnaire; PEQ = Persisting Effects Questionnaire; POMS = Profile of Mood States; QIDS-SR = Quick Inventory of Depressive Symptomatology Self-Report; SDS =. Sheehan Disability Scale; SIGH-A = Structured Clinical Interview Assessment for the Hamilton Anxiety Rating Scale; STAI = Spielberger State Trait Anxiety Inventory; WHO-Qol = WHO Quality of Life BREF.

TABLE S3. Inclusion/Exclusion Criteria, Outcomes, and Adverse Events for Psilocybin Studies in Tobacco Use Disorder

Publication(s)	Key Inclusion Criteria	Key Exclusion Criteria	Primary Outcomes	Secondary Outcomes	Adverse Events
Johnson et al., 2014; Johnson et al., 2017	•Smoking > 10 cigarettes a day •Sufficiently physically healthy •Multiple unsuccessful prior quit attempts •Persistent desire to quit smoking	•Personal or family history of psychosis or bipolar d/o •Current alcohol or drug dependence or h/o in past 5 years	•Urine cotinine levels •Exhaled carbon monoxide •TLFB	•FTCD •QSU •SASE •WSWS •VEQ •Headache interview •Mysticism Scale •SOCQ •PEQ	•N=6 reported strong or extreme fear, fear of insanity, and feeling trapped •Eight (of 10 assessed) reported mild-to-moderate severity headaches occurring ~6 hours after administration. •N=1 reported reliving traumatic experiences from childhood during first dosing session; she was referred out for counseling

d/o = disorder; FTCD = Fagerstrom Test for Cigarette Dependence; h/o = history of; MEQ-30 = 30-item Mystical Experience Questionnaire; mg = milligrams; PEQ = Persisting Effects Questionnaire; QSU = Questionnaire on Smoking Urges; SASE = Smoking Abstinence Self Efficacy; SOCQ = States of Consciousness Questionnaire; TLFB = Timeline Follow Back; WSWS = Wisconsin Smoking Withdrawal Scale; VEQ = Visual Effects Questionnaire.

TABLE S4. Inclusion/Exclusion Criteria, Outcomes, and Adverse Events for Psilocybin Studies in Alcohol Use Disorder

Publication(s)	Key Inclusion Criteria	Key Exclusion Criteria	Primary Outcomes	Secondary Outcomes	Adverse Events
Bogenschutz et al., 2015	•DSM-IV diagnosis of alcohol dependence •2 heavy drinking days in past 30 •Current concerns about drinking behavior •Not currently in treatment	•Personal or family history of psychosis, bipolar d/o, or suicide •Current cocaine, opioid, or stimulant dependence • > 10 lifetime uses of psychedelics •Any psychedelic usage in past 30 days	•TLFB •Heavy drinking days defined as 5 or more drinks for males or 4 or more drinks for females (1 drink = 14g of alcohol) •Drinking days defined by consumption of any alcoholic beverage (even a sip).	•HRS •5D-ASC •SOCQ •ARCI •MSRF •SOCRATES-8A •AASE •PACS •POMS •PEQ •HMS •ASPIRES Spiritual Transcendence Scale •Brief Multidimensional Measure of Religiousness/Spirituality •NEO-PI 3 •SVS	•N=5 mild headaches that resolved within 24 hours •N=1 nausea or vomiting •N=1 aggravation of irritable bowel syndrome with diarrhea •N=1 mild insomnia
Bogenschutz et al., 2022	•DSM-IV diagnosis of alcohol dependence •4 heavy drinking days in past 30	•Medical conditions (e.g., seizure disorder, coronary artery disease) •Personal or family history of psychosis, or bipolar d/o •Major psychiatric conditions (current MDD, PTSD) •Other substance use disorders (except nicotine) •Psychiatric meds or others not compatible with psilocybin •Hallucinogen use in past year or > 25 lifetime uses •Current AUD treatment	•TLFB •% Heavy drinking days from weeks 5-32	•% drinking days from weeks 5-32 •Mean drinks per day •Dichotomous outcomes (Abstinence, Lack of heavy drinking days, Reduction in WHO risk level)	•204 AEs reported •119 in psilocybin group •85 in diphenhydramine group •3 serious AEs, all in diphenhydramine group •N=21 in psilocybin group experienced headaches (43.8% vs. 4.4% in diphenhydramine group) •Anxiety and nausea also more common in psilocybin vs. diphenhydramine group
Heinzerling et al., 2023	•DSM-5 diagnosis of alcohol use disorder, moderate to severe •At least 4 heavy drinking days in the past 30 days	•CIWA-Ar > 7 with negative breathalyzer test •Women who are pregnant or nursing •Unable/unwilling to discontinue outside alcohol treatments except for self-help •Current major depressive disorder or generalized anxiety disorder	•Feasibility, safety, and tolerability of Visual Healing procedure as measured by recruitment/retention rates, minutes of film viewed, adverse events, and vital signs.	•Effects of Visual Healing manipulation on alcohol use disorder outcomes assessed by TLFB and PROMIS Alcohol Use Short Form	•AEs mild to moderate •2 serious AEs, both occurring in 1 individual; severe alcohol intoxication requiring treatment in the emergency department both prior to first dosing session and in weeks following first dosing session •Headache (N=16)

		•Use of serotonergic medications, opioids, or benzodiazepines •Psychedelic use in the past 12 months or > 25 lifetime uses •Medical conditions contraindicated for psilocybin •Personal history or first degree relative with history of psychotic or bipolar disorder •Nicotine or drug use disorder •Active suicidal ideation with at least some intent to act in the past month or any suicidal behavior in past 12 months			•Elevated blood pressure (N=10) •Nausea (N=8) •Twitching (N=5) •Anxiety (N=4) •Feeling flushed (N=3) •Tachycardia (N=3)

5D-ASC = 5 Dimensional Altered States of Consciousness Scale; AASE = Alcohol Abstinence Self Efficacy; ARCI = Addiction Research Center Inventory; AEs = adverse events; CIWA-AR = Clinical Institute Withdrawal Assessment – Alcohol Revised; d/o = disorder; h/o = history of; hrs = hours; HRS = Hallucinogen Rating Scale; HMS = Hood Mysticism Scale; MDD = major depressive disorder; MSRF = Monitor Session Rating Form; NEO-PI-3 = NEO Personality Inventory 3; PEQ = Persisting Effects Questionnaire; PACS = Penn Alcohol Craving Scale; POMS = Profile of Mood States; Prep = preparation; PROMIS = Patient Reported Outcomes Measurement Information System; PTSD = posttraumatic stress disorder; SOCQ = States of Consciousness Questionnaire; SOCRATES-8A = Stages of Change Readiness and Treatment Eagerness Scale; SVS = Schwartz Value Survey; TLFB = Timeline Follow Back; WHO = World Health Organization.

TABLE S5. Inclusion/Exclusion Criteria, Outcomes, and Adverse Events for Psilocybin Studies in Major Depressive Disorder

Publication(s)	Key Inclusion Criteria	Key Exclusion Criteria	Primary Outcomes	Secondary Outcomes	Adverse Events
Carhart-Harris et al. 2016; Carhart-Harris et al. 2018	•Moderate-to-severe MDD (score of > 17 on the 21-item HAM-D) •No improvement on 2 prior trials of antidepressant treatment in the current episode.	•Personal or family h/o psychosis or bipolar d/o •Medical conditions rendering participation unsafe •H/o serious suicide attempts (requiring hospitalization) • Current alcohol or drug dependence •Positive pregnancy test	•Patient-rated intensity of psilocybin experience (0 to 1) •AEs	•QIDS-SR change from baseline to 1 week following high dose •HAM-D •MADRS •BDI •STAI-T •SHAPS	•N=12 transient anxiety •N=9 transient confusion •N=4 transient headache •N=2 transient paranoia
Davis et al., 2020; Gukasyan et al. 2022	•Moderate-to-severe MDD (as assessed by GRID-HAM-D $\geq$ 17) •Not taking medications for depression or willing to discontinue •Agree to not initiate antidepressant treatment for 4 months after enrollment	•Medical conditions rendering participation unsafe •Personal or family h/o psychosis, or bipolar d/o •Not pregnant or nursing •Alcohol or substance use d/o (including nicotine) •Recent ketamine or psychedelic use or > 10 lifetime uses •Psychiatric d/o that may interfere with rapport building •H/o of medically significant suicide attempt •Failure to respond to ECT during current episode •MRI contraindication	•GRID-HAM-D score at baseline, week 5, and week 8 Response defined as $\geq$ 50% reduction in GRID-HAM-D score from baseline Remission defined as GRID-HAM-D score $\leq$ 7	•QIDS-SR •BDI •PHQ-9 •HAM-A •STAI •CSSRS	•No serious AEs •N=1 transient, self-resolving increase in blood pressure •Feeling like crying (92%) •Sadness (79%) •Emotional and/or physical suffering (77%) •Feeling one's heart beating (71%) •Body shaking or trembling (67%) •Pressure or weight on chest or abdomen (67%) •Transient headache during session (33%) or 1-2 weeks after (29%)
Carhart-Harris et al., 2021	•Moderate-to-severe MDD (score of > 17 on the 21-item HAM-D)	•Medical conditions rendering participation unsafe •Personal or family h/o psychosis •H/o serious suicide attempts (requiring hospitalization) •Positive pregnancy test •MRI or SSRI contraindication	•QIDS-SR change from baseline to 6 weeks after first dosing session	•QIDS-SR response at 6 weeks ($\geq$ 50% reduction) •QIDS-SR remission at 6 weeks ($\leq$ 5) •QIDS-SR change from baseline to 1 day after first dosing session •Change in BDI-1A, MADRS, and HAM-D from baseline to 6 weeks after first dose	•No serious AEs •AE prevalence similar in psilocybin (87%) and escitalopram arms (83%) •Higher reporting of increased anxiety and dry mouth in escitalopram arm •AEs in psilocybin arm typically occurred with 24 hrs. of dosing and were most frequently headache

		•Previous use of escitalopram •Psychiatric d/o that may interfere with rapport building			(66.7%) and nausea (26.7%)
Goodwin et al., 2022	•Age 18 or older •DSM-5 diagnosis of major depressive disorder, single episode or recurrent (based upon MINI) • Moderate-to-severe MDD (score of > 17 on the HAM-D) •No response to 2-4 prior trials of antidepressant medication of adequate dose and duration •Free from antidepressant medication for at least 2 weeks	•H/o of psychosis, bipolar d/o, paranoid personality d/o, and borderline personality d/o •Prior ECT or ketamine treatment in current episode •Current CBT that will not remain stable throughout study •Current alcohol or drug dependence or in past year •Significant suicide risk •Exposure to psilocybin in past year or use of psychedelics in current episode •Pregnant or nursing women •Cardiovascular conditions •Uncontrolled diabetes •Seizure d/o •Any other medical condition that might interfere	•MADRS total score change from baseline to 3 weeks after dosing	•MADRS response (>50% reduction from baseline) at 3 weeks •MADRS remission (< 10) at 3 weeks	•AEs reported separately by severity (mild, moderate, severe) and serious (potentially life-threatening) vs. non-serious •Total AEs 1 day after dosing: 25mg (84%); 10 mg (75%); 1mg (72%) •Most frequent in 25mg group were headache (24%), nausea (22%), dizziness (6%), and fatigue (6%) •Severe AEs 1 day after dosing: 25mg (4%); 10mg (8%); 1mg (1%) •Severe AEs day 2 to week 3: 25mg (9%), 10mg (7%), 1mg (1%) •Serious AEs day 2 to week 3: 25mg (N=2 suicidal ideation; N=2 non-suicidal self-injury); 10mg (N=2 suicidal ideation, N=1 intentional self-injury; N=1 hospitalization for severe depression); 1mg (N=0) •Severe AEs week 3 to 12: 25mg (3%), 10mg (4%), 1mg (0%). •Serious AEs from week 3 to 12: 25mg (N=3 suicidal behavior; N=1 codeine withdrawal; N=1 adjustment d/o with anxiety/depressed mood); 10mg (N=1 intentional self-injury; N=1 depression; N=1 suicidal ideation); 1mg (N=1 intentional self-injury)

Goodwin et al., 2023	•Age 18 or older •DSM-5 diagnosis of major depressive disorder, single episode or recurrent (based upon MINI) •Moderate-to-severe MDD (score of > 17 on the HAM-D) •No response to 2-4 prior trials of antidepressant medication of adequate dose and duration •Currently maintained on a therapeutic dose (with 75% or more adherence over past 6 weeks) and willing to continue same dose for the duration of trial of the following medications: citalopram, escitalopram, fluoxetine, paroxetine, sertraline, vilazodone, and vortioxetine	•H/o of psychosis, bipolar d/o, paranoid personality d/o, and borderline personality d/o •Prior ECT or ketamine treatment in current episode •Currently taking antidepressant medication or augmentation other than a single SSRI •Current CBT that will not remain stable throughout study •Current alcohol or drug dependence or in past year •Significant suicide risk •Exposure to psilocybin in past year or use of psychedelics in current episode •Pregnant or nursing women •Cardiovascular conditions •Uncontrolled diabetes •Seizure d/o •Any other medical condition that might interfere	•MADRS total score change from baseline to 3 weeks after dosing	•MADRS response (>50% reduction from baseline) at 3 weeks •MADRS remission (< 10) at 3 weeks •Change from baseline to 3 weeks in CGI severity score •Proportion of responders on CGI severity at 3 weeks (score of 1 or 2)	•17 AEs reported for 12 participants •No serious AEs •11 of 17 AEs experienced in 9 participants had onset on dosing day •8 AEs resolved on dosing day •6 AEs experienced after dosing day in 4 participants; 4 resolved the same day of onset •Most common was headache (N=6 events in 6 participants; N=4 onset on Day 1 and N=2 on Day 2; N=5 reported mild severity; N=1 reported moderate severity) •N=3 increased blood pressure (N=2 severe and treated with clonidine) N=1 chest heaviness and headache •All AEs resolved by 3 weeks and none had duration longer than 7 days
von Rotz et al. 2023	•DSM-IV diagnosis of mild-to moderate major depressive episode in context of major depressive disorder (based upon MINI) • MADRS score between 10 and 40 •Free from antidepressant medication for at least 2 weeks or 5 half-lives •German-speaking •No current SI with plan or intent •Willingness to refrain from alcohol and other psychoactive substances	•H/o bipolar disorder or psychosis •H/o substance dependence (except nicotine or caffeine) within 3 mo. of enrollment •Comorbid anxiety d/o allowed if not requiring treatment •Family hi/o bipolar or psychosis in first or second-degree relatives •Lifetime h/o hallucinogen use > 10 occasions •Concurrent psychotherapy or medication treatment •Abnormal ECG, BMI, or uncorrected hypo/hyper-thyroid	•MADRS total score change from 5 days prior to dosing to 2 weeks after dosing •BDI total score change from 5 days prior to dosing to 2 weeks after dosing •MADRS and BDI response (>50% reduction from baseline) at 2 weeks •MADRS and BDI remission (< 10) at 2 weeks	•SCL-90R •HAM-A •CGI •CSSRS •ASC	•All AEs reported to be mild in severity •Excluded acute, transient effects of psilocybin •In psilocybin arm, these included headache (N=4), dizziness (N=2), nausea (N=1), and diarrhea (N=1)

		•Pregnant or breast-feeding women •MRI contraindication			
Raison et al., 2023	•Age 21-65 y.o. •Women of child bearing potential must agree to use birth control •MADRS score ≥ 28 at baseline and ≤ 30% improvement from screening to baseline •MADRS score difference at screening and baseline ≤ 7	•Pregnant or intention to become pregnant •Unable/unwilling to d/c formal psychotherapy or prohibited medications •Previous history of deep brain stimulation or vagus nerve stimulation •Currently receiving electroconvulsive therapy or repetitive transcranial magnetic stimulation •Use of a psychedelic in the previous five years or > 10 times in lifetime •Cardiovascular conditions contraindicated for psilocybin •Uncontrolled hypertension •Epilepsy •Type I diabetes •Positive urine drug screen •Diagnosis of psychotic or bipolar disorder, or history of these diagnoses in first-degree relatives •Moderate or severe alcohol/drug use disorder, or alcohol/drug use disorder in the past 12 months •Significant suicide risk	•MADRS change from baseline to day 43	•MADRS change from baseline to day 8 •SDS change from baseline to day 43 •Proportion of patients with a sustained depressive symptom response •Proportion of patients with sustained depression remission	•Treatment-emergent AEs occurred in 82% of psilocybin arm and 44% of niacin group •N=3 serious AEs (nephrolithiasis; incisional hernia, obstructive; and appendicitis), 1 in psilocybin arm and 2 in niacin arm •Severe treatment-related AEs in N=4 in psilocybin group (migraine, headache, illusion, panic attack/paranoia) •Rates of mild/moderate AEs higher in psilocybin group vs. niacin •Solicited AEs also higher in psilocybin (76%) vs. niacin (30%) •Headache (N=33 in psilocybin; N=13 in niacin) •Nausea (N=24 in psilocybin; N=3 in niacin) •Visual perceptual effects on dosing day (N=22 in psilocybin; N=3 in niacin) •Visual perceptual effects after dosing day (N=3 in psilocybin; N=0 in niacin) •No suicidal or self-injurious behavior; all suicidal ideation considered passive •Participants reporting an increase in suicidal ideation from baseline to end of trial (N=1 in psilocybin; N=5 in niacin)
Sloshower et al., 2023	•18-65 years old •Meeting DSM-5 criteria for major depressive disorder •Current moderate-to-severe major depressive episode (defined as score	•Primary psychiatric diagnosis other than MDD •Active substance use disorder	•GRID-HAM-D score 1 day before and 2 weeks following each dosing session	•QIDS-SR •HAM-A •RAND 36-item health survey	•1 serious AE: a participant sought hospitalization about two weeks after psilocybin for worsening depression

	of 17 or more on GRID-HAM-D at baseline). •Failed at least one antidepressant trial of adequate dose/duration during current episode.	•Past personal or family history of psychosis or bipolar disorder •Significant or unstable medical or neurological disease •Psilocybin exposure in the past year			•Number of AEs significantly higher after psilocybin vs. placebo •Most common: Mild-to-moderate headache (N=7) Mild-to-moderate anxiety (N=7) Dysphoria (N=3)

5D-ASC = 5 Dimensional Altered States of Consciousness Scale; AEs = adverse events; ASC = Altered States of Consciousness Questionnaire; BDI = Beck Depression Inventory; d/o = disorder; CBT = cognitive behavioral therapy; CGI = Clinical Global Impression; CSSRS = Columbia Suicide Severity Rating Scale; ECT = electroconvulsive therapy; GRID-HAM-D = structured clinical interview version of Hamilton Rating Scale for Depression; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Rating Scale for Depression; h/o = history of; MADRS = Montgomery Asberg Depression Rating Scale; MDD = major depressive disorder; mg = milligrams; MRI = magnetic resonance imaging; PHQ-9 = Patient Health Questionnaire 9; QIDS-SR = Quick Inventory of Depressive Symptomatology Self Report; SCL-90R = Symptom Checklist 90 Revised; SDS = Sheehan Disability Scale; SHAPS = Snaith Hamilton Pleasure Scale; SSRI = selective serotonin reuptake inhibitor; STAI-T = Spielberger State Trait Anxiety Inventory-Trait Form.

TABLE S6. Inclusion/Exclusion Criteria, Outcomes, and Adverse Events for Demoralization in Long-Term AIDS Survivors

Study	Key Inclusion Criteria	Key Exclusion Criteria	Primary Outcomes	Secondary Outcomes	Adverse Events
Anderson et al., 2020	•Homosexual cis-gender males > 50 years old living with HIV •Self-reported acquisition of HIV prior to widespread availability of protease inhibitors •Moderate-to-severe demoralization (Demo. Scale II score > 8)	•Regular psychiatric med use or use of efavirenz •Life expectancy < 6 mo. •Poor functional status experience •Major cognitive impairment •Hi/o psychosis, bipolar d/o, hallucinogen use d/o, narcissistic personality d/o, or HPPD •Current severe MDE •SI with intent in last 3 mo. or suicide attempt in last 2 yrs •Seizure d/o •Current CNS metastases or. Infection •Medical issues rendering participation unsafe	•Rates of recruitment and retention •Qualitative data from focus group •Safety as assessed by CSS-RS, AEs, and CEQ •Participant perceptions of benefits and harms (Likert scale 0-7)	•Change in Demoralization Scale II score from baseline to end of treatment with “last week” recall period •PCL-5 •ICG-R •CESD-R •CGI-S •MQol-R •STAI •MEQ-30	•N=14 had AEs of moderate severity •N=7 had severe AEs •Moderate-to-severe anxiety (N=8) •Paranoia (N=4) •Transient thought d/o (N=1) •Self-limited severe asymptomatic hypertension (N=4) •Self-limited moderate asymptomatic hypertension (N=8)

AEs = adverse events; AIDS = acquired immune deficiency syndrome; CEQ = Challenging Experiences Questionnaire; CESD-R = Center for Epidemiological Studies Depression Scale – Revised; CGI-S = Clinical Global Impressions Scale – Severity of Illness; CNS = central nervous system; d/o = disorder; CSS-RS = Columbia Suicide Severity Rating Scale; HIV = human immunodeficiency virus; HPPD = hallucinogen persisting perception disorder; h/o = history of; ICG = Inventory of Complicated Grief – Revised; MDE = major depressive episode; MEQ-30 = 30-item Mystical Experience Questionnaire; MQoL-R = McGill Quality of Life Questionnaire – Revised; PCL-5 = PTSD Checklist for DSM-5; SI = suicidal ideation; STAI-T = Spielberger State Trait Anxiety Inventory.

TABLE S7. Inclusion/Exclusion Criteria, Outcomes, and Adverse Events for Psilocybin Studies in Eating Disorders

Publication(s)	Key Inclusion Criteria	Key Exclusion Criteria	Primary Outcomes	Secondary Outcomes	Adverse Events
Peck et al., 2023	•Age range of 18-40 •Meeting DSM-5 Diagnostic criteria for anorexia nervosa (restricting or binge-purging subtypes) within a current episode or in partial remission	•BMI < 16kg m^{-2} •Medical instability •Positive pregnancy test •Medical contraindications for psilocybin •Current or previous psychotic or bipolar d/o diagnosis •Substantial suicide risk •Current or past-year substance use dio •Positive screening for borderline personality d/o	•Vital signs •ECG •Suicidality •AEs	•EDE subscales •Body mass index •PASTAS •STAI-T •YBC-EDS	•Headache (N=8) •Fatigue (N=7) •Nausea (N=3) •Feeling abnormal (N=2) •Migraine (N=2) •Dizziness (N=2) •Illusion (N=2) •Pain (N=1) •Anxiety (N=1) •Orthostatic heart rate increase (N=1) •Abdominal pain upper (N=1)

d/o = disorder; ECG = electrocardiogram;; EDE = Eating Disorder Examination; h/o = history of; PASTAS = Physical Appearance State and Trait Anxiety Scale; STAI-T = Spielberger State Trait Anxiety Inventory Trait Form; YBC-EDS = Yale Brown Cornell Eating Disorders Scale