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Psilocybin

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Psilocybin: From Psychiatric Pariah to Perceived Panacea

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Psilocybin: From Psychiatric Pariah to Perceived Panacea

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Objective: The authors critically examine the evidence base for psilocybin administered with psychological support/therapy (PST) in the treatment of psychiatric disorders and offer practical recommendations to guide future research endeavors.

Methods: PubMed was searched for English-language articles from January 1998 to November 2023, using the search term “psilocybin.” A total of 1,449 articles were identified and screened through titles and abstracts. Of these, 21 unique open-label or randomized controlled trials (RCTs) were identified that examine psilocybin for the treatment of obsessive-compulsive and related disorders (N=2), anxiety/depression associated with a cancer diagnosis (N=5), major depressive disorder (MDD; N=8), substance use disorders (N=4), anorexia (N=1), and demoralization (i.e., hopelessness, helplessness, and poor coping) in AIDS survivors (N=1).

Results: The most developed evidence base is for the treatment of MDD (three double-blind RCTs with positive

signals spanning a range of severities). However, the evidence is tempered by threats to internal and external validity, including unsuccessful blinding, small samples, large variability in dosing and PST procedures, limited sample diversity, and possibly large expectancy effects. Knowledge of mechanisms of action and predictors of response is currently limited.

Conclusions: The evidence is currently insufficient to recommend psilocybin with PST as a psychiatric treatment. Additional rigorously designed clinical trials are needed to definitively establish efficacy in larger and more diverse samples, address dosing considerations, improve blinding, and provide information on mechanisms of action and moderators of clinical response. Head-to-head comparisons with other evidence-based treatments will better inform the potential future role of psilocybin with PST in the treatment of major psychiatric disorders.

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Psilocybin is an indolylalkylamine (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) psychedelic prodrug produced by more than 200 species of fungi (1) distributed across all continents (except Antarctica). It is rapidly dephosphorylated upon ingestion to its active metabolite, psilocin (4-hydroxy-N,N-dimethyltryptamine) (2), the chemical moiety responsible for psychoactive effects. Psilocin is a lipophilic compound that produces hallucinatory effects via functionally selective agonism of the serotonin (5-HT) 2A receptor (3). Agonism occurs at numerous other monoamine receptors (including 5-HT_{1A}, 5-HT_{2B}, and 5-HT_{2C} receptors), which may contribute distinctive effects relative to other psychedelics and nonpsychedelic 5-HT_{2A} agonists (4, 5).

Psilocybin ingestion induces transient and highly variable effects across cognitive, affective, and perceptual domains. The 4–6 hour time course of subjective effects closely mirrors the bioavailability of active compounds, plasma half-life, and duration of time the drug occupies the 5-HT_{2A}

receptor (6, 7). Reported effects include acute changes in emotional processing; alterations in sense of self; changes in sensory perception (including visual and auditory illusions, distortions, and/or hallucinations); psychomotor slowing; shifts in attention, working memory, and executive function; and, at times, profound states of consciousness, termed “mystical experiences,” characterized by a sense of unity, ineffability, and deep reverence for life, oneself, and the world (8–10).

Psilocybin delivered with psychotherapy or psychological support is often referred to as “psilocybin-assisted therapy” or “psilocybin-assisted psychotherapy.” In this review, we refer to this approach as “psilocybin with psychological support/therapy” (psilocybin with PST) to maintain an agnostic position regarding the centrality of the drug versus psychological components in facilitating therapeutic change (11). It involves the administration of psilocybin in one or more sessions supervised by a therapist or

co-therapist team (12–14). During the first phase (preparation), the patient meets with the therapist(s) for psychoeducation and informed consent. In the second phase (dosing), psilocybin is administered, and the patient is encouraged to rest in a comfortable position, wear headphones and eyeshades, and focus their attention inward. Sessions typically commence in the morning to accommodate the full duration of psilocybin's effects, with a peak onset of effects at 60–90 minutes after ingestion. After the effects of psilocybin have abated, the participant is released into the care of a relative or friend or observed overnight in an aftercare setting. In the third phase (integration), the patient meets with the therapist(s) for a debriefing to discuss the experience, adverse effects, and/or safety issues. Therapist(s) may offer additional guidance to aid the participant in coming to a subjective sense of insight regarding the experience (15). The process typically occurs over the course of 1–4 weeks, depending on the number of planned dosing sessions (12–14).

Although initially the mechanistic and therapeutic study of psilocybin and other psychedelic compounds was largely a very specialized focus of investigation led by a select cadre of investigators, accumulating evidence in the past decade has generated an enormous surge of interest (16). Several studies have reported therapeutic benefits of psilocybin with PST in major depressive disorder (MDD) (12–14, 17, 18), alcohol and tobacco use disorders (19–21), and anxiety and depression associated with life-threatening illness (22–25). These reports have generated substantial media interest and enthusiasm, but it remains unclear whether the high degree of interest is warranted. Our aims in the present review were to critically evaluate the evidence base for psilocybin with PST in the treatment of psychiatric disorders, focusing on open-label and randomized controlled trials (RCTs) that report on acute and long-term effects, and to offer recommendations for improving the breadth and quality of the evidence base for psilocybin with PST in psychiatry.

METHODS

We sought to identify peer-reviewed publications in which one or more doses of psilocybin were administered with PST to a well-defined psychiatric sample for therapeutic purposes. We focused our literature search on open-label or randomized controlled trials published in the past 25 years. A search was conducted in PubMed for English-language articles from January 1998 to November 2023 using the search term “psilocybin.” A total of 1,449 articles were identified and screened by one author (G.A.F.) through article titles, abstracts, and full texts. Inclusion criteria included 1) reporting on acute or long-term primary clinical outcomes from administration of one or more doses of psilocybin in the context of PST by trained providers in a controlled setting to a clearly defined group of individuals for the purposes of examining improvements in psychiatric or mental health

outcomes using a validated outcome measure; and 2) full-text peer-reviewed article available in English (a supplemental CSV file with the complete list and classifications is provided with the materials in the online supplement). Reviews, meta-analyses, opinion pieces, case studies, pre-clinical studies, observational studies, experimental reports in healthy individuals, and studies that report on non-clinical secondary outcomes (e.g., neuroimaging changes) were excluded from the primary review of clinical studies. See the Supplemental Review section in the online supplement for an extended discussion of pharmacokinetics and pharmacodynamics, acute and long-term nonclinical effects in healthy and clinical samples, and the typical model of PST.

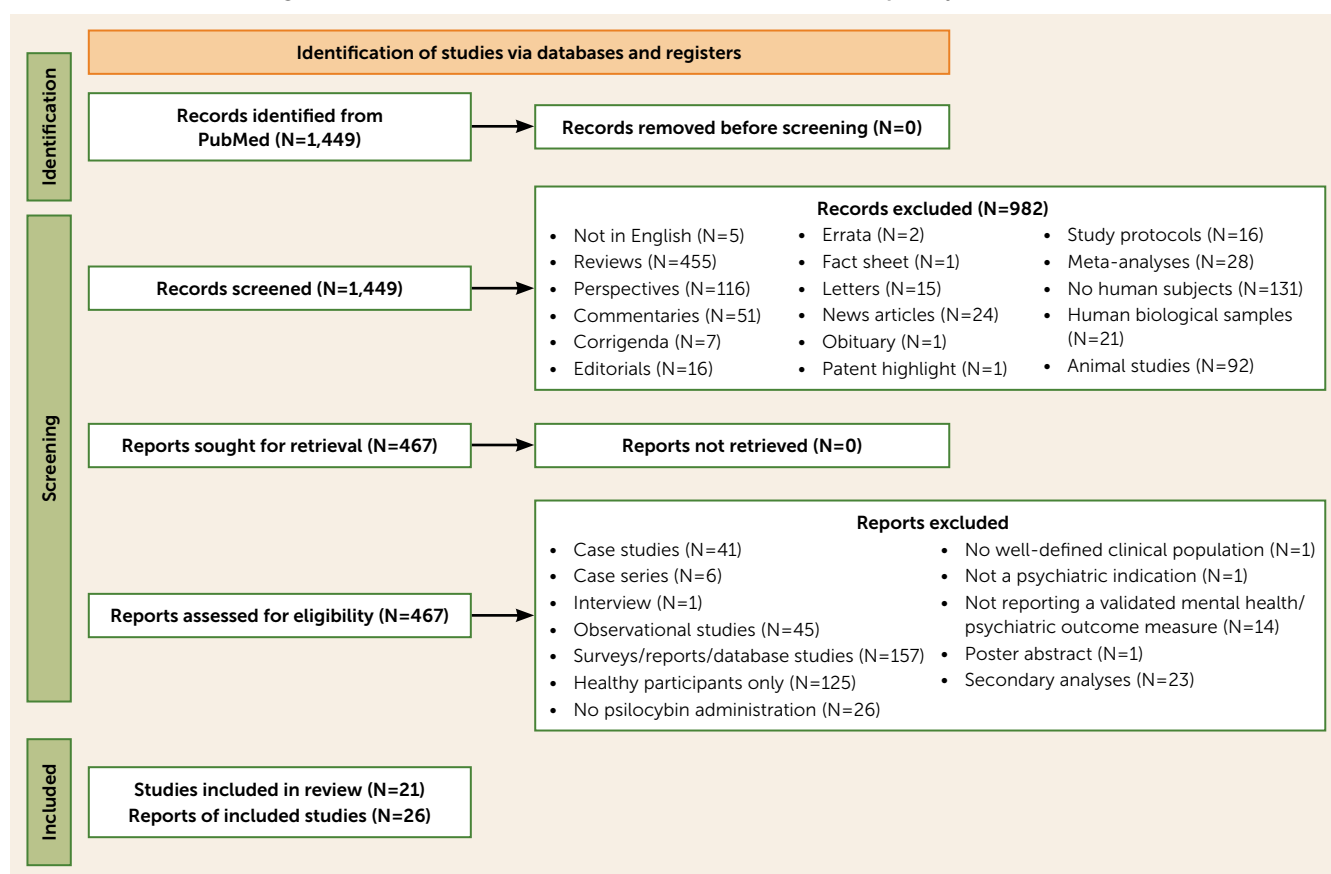
RESULTS

We identified 21 unique open-label trials or RCTs with 26 publications describing acute and/or long-term primary clinical outcomes (Figure 1, Table 1; see also the Supplemental Results section and Tables S1–S7 in the online supplement). We begin by discussing key findings of clinical efficacy and then highlighting important areas of consideration that qualify clinical efficacy findings: dosing, duration of benefits, factors affecting internal validity, factors affecting generalizability, adverse events, psychological treatment components, and predictors of therapeutic response.

Evidence of Efficacy

The most robust evidence base exists in MDD, including treatment-resistant MDD. There have been three parallel-arm RCTs, one in mild to moderate MDD ($N=52$) (26), one in moderate to severe MDD ($N=104$, with ~13% of the sample being treatment-resistant) (18), and the third in treatment-resistant MDD ($N=233$) (27). Each of these studies demonstrated a statistically superior effect of a single psilocybin dose (15–25 mg) with PST versus inactive placebo (26), low-dose psilocybin (1 mg) (27), or 100 mg niacin (active placebo) (18) on the primary outcome measure. Additional, less rigorously designed positive RCTs in MDD include a parallel-arm trial ($N=27$) comparing two doses of psilocybin (20 mg/70 kg and 30 mg/70 kg) in dose-ascending order versus a treatment waiting list condition (13), which demonstrated a statistically superior benefit on the primary depression outcome. A single-arm open-label trial ($N=12$) of 10 mg and 25 mg psilocybin with PST in dose-ascending order was the first to demonstrate evidence of possible efficacy (12). However, from existing data, it is clear that a subset of individuals demonstrate a lack of response both acutely and long-term. There was one negative parallel-arm RCT ($N=59$) comparing two 25-mg doses of psilocybin plus daily pill placebos versus 1 mg psilocybin plus 10–20 mg escitalopram, with both groups receiving PST (14). Although secondary outcomes favored psilocybin, the two arms did not differ on the prespecified primary outcome measure. A

FIGURE 1. PRISMA flow diagram of the literature search and inclusion and exclusion of psilocybin trials



subsequent open-label trial of 25 mg psilocybin in participants with treatment-resistant MDD maintained on selective serotonin reuptake inhibitor (SSRI) monotherapy (N=19) (28) demonstrated a safety and efficacy profile very similar to that in patients who were tapered off antidepressants (27). A within-subject, placebo-controlled, fixed-order study of 25 mg psilocybin (preceded by placebo) in 15 participants with MDD failed to demonstrate statistically significant differences in symptom change following psilocybin versus placebo, although effect sizes were larger following psilocybin (29).

Evidence of efficacy has also been demonstrated in anxiety and depression associated with a life-threatening cancer diagnosis in the context of less rigorous crossover or open-label trial designs. There have been two positive crossover trials examining a single dose of 22–30 mg/70 kg psilocybin versus 1–3 mg/70 kg psilocybin (N=56) (23) or 21 mg/70 kg psilocybin versus 250 mg niacin (N=31) (24), both demonstrating statistically superior benefits on anxiety and depression outcomes prior to crossover in individuals receiving the active versus comparator treatment. An earlier, smaller crossover trial in this population comparing 0.2 mg/kg psilocybin versus 250 mg niacin in 12 participants demonstrated effects for superiority of the active treatment condition that fell short of statistical

significance (22). Two more recent trials, both open-label, in which 25 mg psilocybin was administered with either complete or partial group-based PST for depression in the context of a cancer diagnosis, also demonstrated evidence for statistically significant reductions on primary outcomes following treatment (30–32).

The only other clinical indication with at least one published RCT is alcohol use disorder (AUD). There has been one trial (N=95) examining two doses of psilocybin with PST in dose-ascending order (25 mg/70 kg followed by 30 or 40 mg/70 kg, depending on subjective experience in the first dosing session) versus two dose-ascending sessions with diphenhydramine hydrochloride (50 mg followed by 100 mg; an antihistamine used as an active placebo) (21). This study demonstrated a statistically superior reduction for psilocybin versus diphenhydramine on monthly percentage of heavy drinking days over the 32 weeks following the first study drug administration. The study was informed by an earlier small, single-arm, open-label trial in AUD (N=10) demonstrating a similar benefit of two doses of psilocybin (21 mg/70 kg and 28 mg/70 kg) administered in ascending order (19). A recent open-label study in AUD (N=20) of two doses of 25 mg psilocybin with a randomized setting manipulation (viewing a specialized nature-themed video at the beginning and end of the first dosing session versus standard

dosing with music and eyeshades, with the second dosing session procedure at the participant's discretion) demonstrated overall improvements in AUD symptoms that were similar across study arms, although participants who were randomized to the nature video showed lower psilocybin-induced increases in blood pressure (33).

Initial positive findings have also been demonstrated in other clinical indications in the context of single-arm, open-label trials. These include an early within-subject dose-comparison trial in obsessive-compulsive disorder (N=9) (34); an open-label trial in tobacco dependence (N=15); an open-label trial in older long-term male survivors of AIDS (N=18) suffering from demoralization (39); an open-label feasibility trial for anorexia nervosa (N=10) (35); and an open-label trial (N=12) for treatment-resistant body dysmorphic disorder (36).

Dosing Considerations

Dosing schemes have varied greatly, with a primary source of variation being weight-adjusted versus fixed dosing (Table 1). In 11 of 21 reviewed trials, dosing was based on body weight, with doses ranging from 1 mg/70 kg (a low/inactive comparator dose) to 40 mg/70 kg (a very high dose administered in a dose-ascending design). The other 10 trials have used fixed dosing, with 25 mg generally used as the active dose in single-dosing-session studies. One trial used fixed dosing in a dose-ascending order, beginning with 10 mg followed by 25 mg. Early trials overwhelmingly utilized weight-based dosing (the first seven of eight published studies), whereas later studies, particularly in MDD, have begun to adopt fixed-dosing schemes. Only MDD has multiple published trials with both weight-based and fixed dosing, although these approaches have not been directly compared. Effective weight-based doses in MDD appear to range from 15 mg/70 kg for mild to moderate MDD (26) to 30 mg/70 kg for moderate to severe MDD (13). Fixed-dosing schemes have generally favored a 25-mg dose in MDD, which has shown superiority relative to 1 mg psilocybin (27) and 250 mg niacin (18) but not 10 mg psilocybin (27) or 10–20 mg/day escitalopram (14). The majority of trials (14 of 20) have administered a single dose of psilocybin, but a substantial number (seven of 21) have administered more than one active dose (usually two doses, but one trial has administered three). To date, the effect of number of dosing sessions on clinical outcomes has not been rigorously tested, and superiority of multiple doses versus a single dose remains an open question. Microdosing—that is, the more frequent administration (e.g., several days a week) of low doses of psychedelic compounds with sub-psychedelic effects for the promotion of health benefits—is an increasingly popular trend and has started to undergo investigation in healthy individuals (37, 38). However, at the time of our literature review, there were no controlled studies assessing effects of psilocybin microdosing on therapeutic outcomes for any mental health condition.

Duration of Benefits

Existing RCTs have only variably reported on benefits beyond acute clinical endpoints. Across indications, acute clinical endpoints have ranged from 1 day to around 12 weeks (13, 18, 22, 28, 31, 33, 35, 36, 39), with longer-term follow-up outcomes assessed over several months (27, 29, 30, 39, 40) or 1 or more years (25, 41, 42). However, long-term follow-up assessments of 1 year or more have occurred only in smaller trials with less rigorous study designs, that is, open-label pilot studies or crossover trials. Most RCTs have utilized acute clinical endpoints in the range of 1 to 6 weeks (13, 14, 18, 26, 27), especially in crossover designs that necessitate shorter duration of inference (23, 24). A notable exception is the sole RCT of psilocybin for AUD, which examined a primary clinical endpoint of 32 weeks (21). These time frames illustrate a notable advantage of psilocybin with PST, namely, the rapid onset of therapeutic effects. However, long-term durability of these effects (e.g., ≥ 6 months after dosing) has been characterized only in smaller crossover studies of anxiety/depression associated with life-threatening cancer (25) and MDD (41) and small open-label studies of tobacco dependence (42) and MDD (17). In these cases, durability appears substantial. However, both designs limit attribution of long-term benefits to the experimental treatment. The evidence base would clearly benefit from additional characterization of possible long-term durability of RCT treatment effects at 6 months or more. This would help to better contextualize the possible future role of psilocybin with PST amid other existing treatments with demonstrated long-term efficacy and durability.

Factors Affecting Internal Validity

One of the most prominent challenges to internal validity in trials of psychedelic compounds is effectively maintaining blinding (43). In trials of psilocybin with PST, there has been infrequent assessment and reporting of blinding integrity in study participants. The three crossover RCTs in anxiety/depression associated with life-threatening cancer did not formally assess blinding in study participants, but one study noted that drug administration order was apparent to both participants and study staff, suggesting functional unblinding (22). The other two RCTs tracked study therapists' assessment of drug condition for each dosing session and noted that session staff could generally distinguish between treatment conditions and drug doses with a high degree of accuracy (23, 24). None of the blinded parallel-arm RCTs in MDD have assessed or reported on blinding success in either study participants or treatment facilitators (14, 18, 26, 27). The trial of psilocybin versus diphenhydramine for AUD is a notable exception (21), as it did assess and report on blinding success. This revealed that ~93%–97% of both study participants and study therapists correctly distinguished between psilocybin and diphenhydramine at each dosing session. The assessment and reporting of blinding success in both participants and providers represents a notable advancement in methodological rigor, but one can

TABLE 1. Summary of psilocybin trials^a

Indication	Publication	Design	Dosing Sessions	Psilocybin Doses	Comparator
Obsessive-compulsive disorder	Moreno et al., 2006 (34)	Open-label trial	4 dosing sessions, 1 week apart	Very low (0.025 mg/kg), low (0.1 mg/kg), medium (0.2 mg/kg), high (0.3 mg/kg)	None
Anxiety or depression due to cancer	Grob et al., 2011 (22)	Within-subject, double-blind, placebo-controlled crossover RCT	2 dosing sessions, a few weeks apart	0.2 mg/kg	250 mg niacin
Tobacco dependence	Johnson et al., 2014 (20); Johnson et al., 2017 (42)	Open-label trial	3 dosing sessions, 2–6 weeks apart; began with moderate dose, proceeded to high doses in 2nd and 3rd dosing sessions if participant could tolerate	Moderate (20 mg/70 kg), high (30 mg/70 kg)	None
Alcohol dependence	Bogenschutz et al., 2015 (19)	Open-label trial	2 dosing sessions, 4 weeks apart; began with moderate dose, proceeded to high dose in 2nd session if participant could tolerate and did not have complete mystical experience with lower dose	Moderate (21 mg/70 kg), high (28 mg/70 kg)	None
Anxiety or depression due to cancer	Griffiths et al., 2016 (23)	Within-subject, double-blind, placebo-controlled crossover RCT	2 dosing sessions, ~5 weeks between	22 or 30 mg/70 kg	1 mg or 3 mg/70 kg psilocybin
Anxiety or depression due to cancer	Ross et al., 2016 (24); Agin-Liebes et al., 2020 (25)	Within-subject, double-blind, placebo-controlled crossover RCT	2 dosing sessions, ~7 weeks between	21 mg/70 kg	250 mg niacin

^a AUD=alcohol use disorder; BDD-YBOCS=Yale-Brown Obsessive Compulsive Scale Modified for Body Dysmorphic Disorder; BDI=Beck Depression Inventory; CBT=cognitive-behavioral therapy; EDE=Eating Disorders Examination; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale; MDD=major depressive disorder; MET=motivational enhancement therapy; mo.=month; N/A=not applicable; NIH-HEALS=National Institutes of Health Healing Experiences in All Life Stressors; OCD=obsessive-compulsive disorder; QIDS-SR=Quick Inventory of Depressive Symptoms–Self-Report; RCT=randomized controlled trial; SDS=Sheehan Disability Scale; SSRI=selective serotonin reuptake inhibitor; STAI=State-Trait Anxiety Inventory; WHO=World Health Organization; Y-BOCS=Yale-Brown Obsessive Compulsive Scale.

Psychological Support	N Randomized or Enrolled	Duration of Follow-Up	N Completed Study	Blinding Assessment and Success	Summary of Results
Prep: screening and day before; dosing: music and eyeshades; after: debrief at unspecified point	N=9 (7 male, 2 female); ages 26–62	24 hours after each dose	N=6 received all four doses	N/A	Main effect of time on Y-BOCS scores; all scores decreased from baseline to post-ingestion assessment; reduction in Y-BOCS scores ranged from 23% to 100%
Prep: unspecified number of sessions; dosing: music and eyeshades; after: debrief at end of session	N=12 (1 male, 11 female); ages 36–58	6 months	N=8 at 6 mo., N=11 at 4 mo., N=12 at 3 mo	Not formally assessed, but drug order noted to be apparent to both participants and investigators	30% reduction in BDI at 1 month ($p=0.05$); became statistically significant at 6-month follow-up ($p=0.03$); trait anxiety showed decrease during follow-up ($p's < 0.03$)
Prep: 4 weekly CBT sessions with 2–3 therapists; dosing: music and eyeshades, guided imagery at end of first dosing; after: weekly support visits between dosing sessions	N=15 (10 male, 5 female)	6 months	N=12 completed all dosing sessions	N/A	12 of 15 participants were nicotine abstinent at 6-month follow-up; 11 of the 12 reported quitting on the target quit date and were verified as abstinent by urine and breath testing at all subsequent assessments during intervention period
7 MET sessions, three preparation sessions, and two integration sessions; prep: 4 sessions with two or three therapists; dosing: music and eyeshades; after: 4 sessions between 1st and 2nd dose, and 4 after 2nd dose	N=10 (6 male, 4 female); ages 25–62	36 weeks	N=10 had one dose, N=7 had two doses, N=9 completed follow-up measures	N/A	Percent drinking days and percent heavy drinking days decreased during weeks 5–12 (after psilocybin) relative to baseline and relative to weeks 1–4 (MET/preparation sessions prior to psilocybin)
Prep: 2 or more sessions (mean of ~3 for ~8 hours total); dosing: music and eyeshades; after: 2+ sessions between 1st and 2nd dosing session (mean of ~3 for ~3 hours) and 2+ sessions between 2nd dose and 6-month follow-up (mean of ~2.5 for ~2.4 hours)	N=56 (26 male, 25 female); mean age, ~56 years	6 months	N=51 had one dose, N=49 had two doses, N=46 completed 6-mo. follow-up	Not assessed in participants, but session monitors could consistently distinguish between doses	Response rates on HAM-D and HAM-A were 75%–83% after dosing session 2; remission rates were 42%–68%; at 6-month follow-up, response rates were 77%–83%, and remission rates were 50%–71%
Prep: three 2-hour sessions with therapist dyad over 2–4 weeks; dosing: music and eyeshades; after: three 2-hour sessions with dyad starting day after dosing	N=31 (11 male, 18 female); ages 22–75, mean age, ~56 years	3–4 years	N=29 had one dose, N=26 had two doses, N=23 completed 6-mo. follow-up, N=16 completed long-term follow-up (3–4 yrs.)	Not assessed in participants, but session monitors could consistently distinguish between drugs	Larger reductions in anxiety and depressive symptoms prior to crossover point for psilocybin versus niacin (all $p's < 0.05$); typically manifested the day following the dosing session and were sustained up to 7 weeks post-dosing; large effect sizes across all measures and time points ($0.8 < d < 1.69$); at long-term follow-up, response rates were 57%–79% across measures

continued

TABLE 1, *continued*

Indication	Publication	Design	Dosing Sessions	Psilocybin Doses	Comparator
Treatment-resistant MDD	Carhart-Harris et al., 2016 (12); Carhart-Harris et al., 2018 (17)	Open-label trial	2 dosing sessions, 7 days apart; low dose in first dosing session, treatment dose in second	Low dose (10 mg), treatment dose (25 mg)	None
MDD	Davis et al., 2021 (13); Gukasyan et al., 2022 (41)	Double-blind, waiting-list-controlled parallel-arm RCT	2 dosing sessions, 1–3 weeks apart	Moderately high (20 mg/70 kg), high (30 mg/70 kg)	Waiting list
Demoralization in long-term AIDS survivors	Anderson et al., 2020 (39)	Open-label trial	1 dosing session	21 mg/70 kg for cohort 1, 25.2 mg/70 kg for cohorts 2 and 3	None
MDD	Carhart-Harris et al., 2021 (14)	Double-blind, placebo-controlled parallel-arm RCT	2 dosing sessions, 3 weeks apart	2 active doses (25 mg) plus daily placebo	2 inactive doses of psilocybin (1 mg) plus escitalopram 10–20 mg/day
Alcohol dependence	Bogenschutz et al., 2022 (21)	Double-blind, placebo-controlled, parallel-arm multi-site RCT	2 dosing sessions, 4 weeks apart; began with moderate dose, proceeded to high dose in 2nd session if participant could tolerate it and agreed to increase; second dose was 40 mg/70 kg if participant did not have complete mystical experience with lower dose; otherwise it was 30 mg/70 kg	Moderate 1st dose (25 mg/70 kg), high 2nd dose (30 mg/70 kg or 40 mg/70 kg)	Diphenhydramine, 50 mg (1st dose), 100 mg (2nd dose)

Psychological Support	N Randomized or Enrolled	Duration of Follow-Up	N Completed Study	Blinding Assessment and Success	Summary of Results
Prep: 4 hours on a single visit with two psychiatrists; dosing: music and eyeshades; after: phone call 1 day after low dose; in-person therapy 1 day and 1 week after second treatment dose	N=12 in 2016 paper (6 male, 6 female); N=20 in 2018 paper (14 male, 6 female); ages 30–64	6 months	N=12 completed in 2016 paper; N=19 completed all measures	N/A	Mean self-reported intensity of psilocybin effects was 0.51 for the 10-mg dose and 0.75 for the 25-mg dose; psilocybin was well tolerated with no serious or severe adverse events; QIDS-SR reduced at all time points; maximal effect 2 weeks after high dose
Two facilitators; prep: 8 hours over 2 weeks (2 sessions, about 1 week apart); dosing: music and eyeshades; after: 1 session (~2 hours) 3 days after first dosing; a second session (~2 hours) 3 days after second dosing session	N=27; N=15 to immediate treatment, N=12 to waiting list (16 female, 11 male); mean age, 39.8 years	1 year	N=26 received one dose, N=24 received two doses, N=24 completed all measures	N/A	Reduction in HAM-D score for immediate treatment versus waiting list; large effect sizes at 5 and 8 weeks; across both arms, 17 responders at weeks 5 and 8; across both arms, 14 remitters at week 5 and 13 at week 8; rapid reduction in QIDS-SR scores starting 1 day after first dosing session; benefits largely maintained at 3, 6, and 12 months
Two therapists; prep: one 90-min. individual session, 2 weeks of twice-weekly 90-min. group therapy sessions; dosing: music and eyeshades; after: 2-hour individual therapy with at least one therapist the following day, then additional twice-weekly 90-min. group therapy sessions for 2–3 weeks	N=18, 3 cohorts of 6 participants each (all male); ages 50–66	3 months	N=18 received one dose, N=17 completed treatment, N=18 completed follow-up assessments	N/A	Rates of recruitment and retention high (95%); intervention well-tolerated; reduction in Demoralization Scale–II score from baseline to end of treatment and at 3-month follow-up; similar improvements in other outcomes except STAI
Two facilitators; prep: 1 session lasting ~3 hours prior to first dose, and another lasting ~1 hour prior to second dose; dosing: music and eyeshades; after: 3 debriefing sessions after each dose, starting 1 week after each dose and occurring over 3 weeks	N=59; N=30 to 25 mg psilocybin + daily placebo, N=29 to 1 mg psilocybin + 10–20 mg daily escitalopram (20 female, 39 male); mean age, 43.3 years in psilocybin arm, 39.1 years in escitalopram arm	6 weeks	N=24 completed escitalopram protocol, N=27 completed psilocybin protocol	Not assessed	QIDS-SR change from baseline to 6 weeks did not differ between psilocybin and escitalopram arms; all secondary outcomes favored psilocybin, but statistical significance not inferred
META (motivational enhancement and taking action); prep: 4 sessions with 2 therapists; dosing: music and eyeshades; after: 4 sessions between first and second dose, and four after second dose	N=95; N=49 to psilocybin arm, N=46 to diphenhydramine arm (42 female, 53 male); mean age, 46 years	36 weeks	N=93 received one dose, N=78 received two doses, N=88 completed 8-mo. follow-up assessment	93.6% of participants guessed correctly after 1st dose, 94.7% of participants guessed correctly after 2nd dose; therapists guessed correctly 92.4% of the time after 1st dose and 97.4% of the time after 2nd dose	Percent heavy drinking days lower in psilocybin versus diphenhydramine group; psilocybin group more likely to report no heavy drinking days and reduction in WHO risk level

continued

TABLE 1, continued

Indication	Publication	Design	Dosing Sessions	Psilocybin Doses	Comparator
Treatment-resistant MDD	Goodwin et al., 2022 (27)	Double-blind parallel-arm RCT	1 dosing session	25 mg or 10 mg	1 mg
Treatment-resistant MDD (all participants maintained on SSRI monotherapy)	Goodwin et al., 2023 (28)	Open-label trial	1 dosing session	25 mg	None
MDD	von Rotz et al., 2023 (26)	Double-blind parallel-arm RCT	1 dosing session	0.215 mg/kg (considered a moderate dose)	Inactive placebo
Depression due to cancer	Lewis et al., 2023 (30)	Open-label trial	1 dosing session	25 mg	None

Psychological Support	N Randomized or Enrolled	Duration of Follow-Up	N Completed Study	Blinding Assessment and Success	Summary of Results
Lead and assistant therapist for each patient; prep: 3 sessions, with final session 1 day before dosing; dosing: music and eyeshades; after: 2 sessions, one the day after dosing with both therapists, and a second 1 week later with the lead therapist	N=233; N=79 to 25 mg, N=75 to 10 mg, N=79 to 1 mg (121 female, 112 male); mean age, 39.8 years	12 weeks	N=233 received dose, N=210 completed full protocol	Not assessed	Difference on MADRS between 25-mg and 1-mg arms at primary endpoint, with 25 mg being superior to 1 mg; no difference on MADRS between 10-mg and 1-mg arms at primary endpoint; other statistical tests not conducted due to hierarchical testing procedure
Prep: 3 sessions, with final session 1 day before dosing; dosing: music and eyeshades; after: 2 sessions, one the day after dosing, and a second a week later	N=19 (13 female, 6 male); mean age, 42.2 years	3 weeks	N=19 of 24 enrolled participants underwent dosing	N/A	Mean change in MADRS from baseline to week 3, -14.9 (statistically significant); response on MADRS (>50% reduction from baseline) observed in 8 participants (42.1%) at week 3; responders were also all remitters (MADRS score <10) at week 3
A single therapist; prep: 2 hour-long sessions, with final session 1 day before dosing; dosing: music (no mention of eyeshades); after: 3 hour-long sessions, the first the day after dosing, the second 1 week later, and the third 2 weeks later	N=52; N=26 to psilocybin arm, N=26 to placebo arm (33 female, 19 male); mean age, 37.6 years in psilocybin arm, 35.9 years in placebo arm	14 days	N=52 received dose; N=49 completed study	Not assessed	Significant difference for change in MADRS and BDI between arms; average between-arm differences were -13 on MADRS and -10.5 on BDI for psilocybin versus placebo; 58% response rate on MADRS and 54% on BDI in psilocybin arm; 54% remission rate on MADRS and 46% on BDI in psilocybin arm; mean differences between arms on outcomes largest 2 days after dosing
Group psychotherapy format, 1:1 provider to therapist ratio; each cohort involved 4 patients, 4 therapists, 1 lead therapist, and 1 study coordinator (10 in total); prep: three 120-min. group preparation sessions over a 1-week period; dosing: 6–8 hours in a group administration setting with private "bays" for each participant, music provided over speakers; integration: three 120-min. sessions over the 2 weeks following dosing	N=12 (8 female, 4 male); ages 30–71, mean age, 48.2 years	26 weeks	N=12 completed treatment	N/A	Primary HAM-D outcome decreased from baseline to 2-week follow-up primary endpoint and the 26-week long-term endpoint; clinically substantial change in 8 participants (reductions of 7–12 points), and clinically significant change in 3 participants (4–6 points)

continued

TABLE 1, continued

Indication	Publication	Design	Dosing Sessions	Psilocybin Doses	Comparator
Anorexia nervosa	Peck et al., 2023 (35)	Open-label trial	1 dosing session	25 mg	None
MDD	Raison et al., 2023 (18)	Double-blind parallel-arm RCT	1 dosing session	25 mg	100 mg niacin
Body dysmorphic disorder	Schneier et al., 2023 (36)	Open-label trial	1 dosing session	25 mg	None
Depression due to cancer	Agrawal et al., 2023 (32); Shnayder et al., 2023 (31)	Open-label trial	1 dosing session	25 mg	None

Psychological Support	N Randomized or Enrolled	Duration of Follow-Up	N Completed Study	Blinding Assessment and Success	Summary of Results
Prep: two sessions within 10 days of dosing day with a single lead therapist; dosing: two psychologists present; music and eyeshades; integration: two integration sessions, 1 day and 1 week after dosing	N=10	3 months	N=10 received 25 mg psilocybin	N/A	No serious adverse events observed; no clinically significant changes in vital signs or ECG; 2 participants developed hypoglycemia, which resolved within 24 hours; no increases in suicidal ideation and no suicidal behaviors reported at post-dosing follow-up; EDE subscale of weight concerns decreased at 1 month and 3-month follow-up; EDE subscale of shape concerns decreased at 1 month but not 3 months; EDE eating concerns and dietary restraint subscale changes not significant at 1 or 3 months
Prep: 6–8 hours over multiple days with 2 facilitators, with at least 1 session in-person; dosing: music and eyeshades, 7–10 hours in length, two facilitators present; integration: 3 sessions, 1 the day following dosing, 1 a week later, and another 2 weeks after dosing	N=104; N=51 to psilocybin arm, N=53 to niacin arm (52 male, 52 female); mean age, 40.4 years in psilocybin arm, 41.8 years in niacin arm	6 weeks	N=104 randomized, N=103 received assigned dose, N=92 completed all assessments	Not assessed	Greater reductions on primary outcome (MADRS) from baseline to day 43 and from baseline to day 8 for psilocybin versus niacin; more participants receiving psilocybin versus niacin displayed sustained depressive symptom response; mean change in disability score (SDS) from baseline to day 43 greater in the psilocybin versus niacin group; results of per protocol analysis largely similar, except difference in sustained remission became significantly different between psilocybin and niacin arms
Prep: 4 weekly preparatory sessions with two psychotherapists; dosing: 7–8 hours with both therapists; music and eyeshades; integration: 2 sessions, 1 day and 1 week after dosing	N=12 (4 male, 8 female)	12 weeks	N=12 received dose and completed study, N=1 started an antidepressant at week 4	N/A	Significant decrease on BDD-YBOCS from baseline to 12 weeks; 7 participants were responders at week 12, and 4 were sustained remitters
Mixed individual/group psychotherapy format in cohorts of 3–4 patients; preparation: 2-hour individual therapy session with a single therapist, followed by 75-min. group therapy and 45-min. individual therapy the day before dosing; dosing: individual dosing; music and eyeshades; integration: 75-min. group therapy session and 45-min. individual therapy session the day after dosing, followed by the same format 1 week later	N=30 (21 female, 9 male); ages 30–78, mean age, 56.1 years	8 weeks	N=30 completed study	N/A	Reduction in MADRS scores from baseline to 8 weeks; sustained response in 24 patients, with 15 patients demonstrating remission on MADRS; improvements on all three factors of NIH-HEALS beginning the day after dosing and lasting for 8 weeks

continued

TABLE 1, continued

Indication	Publication	Design	Dosing Sessions	Psilocybin Doses	Comparator
MDD	Sloshower et al., 2023 (29)	Within-subject, fixed-order, placebo-controlled trial	2 dosing sessions, 4 weeks apart; placebo dose always preceded psilocybin dose	21 mg/70 kg	Inactive placebo
AUD	Heinzerling et al., 2023 (33)	Pilot open-label trial of two doses of 25 mg psilocybin with a randomized setting manipulation (visual healing, a nature-themed video, vs. standard dosing setting)	2 dosing sessions, 4 weeks apart	25 mg (visual healing vs. standard dosing setting randomized at first dosing session)	No drug comparator

reasonably conclude that all existing blinded RCTs were unsuccessful in maintaining the blind. Thus, lack of effective blinding remains a consistent threat to internal validity.

Related to blinding is the issue of comparator conditions. Existing trials have either used a delayed treatment condition (13), an inactive placebo (26), an active placebo (drugs designed to induce some subjective effect but no therapeutic effect) (18, 21, 22, 24), or a low dose of psilocybin (typically 1–3 mg), which allows for the expectation in study participants for receipt of some amount of active drug in each dosing session but presumably without promotion of substantial psychoactive or therapeutic effects (14, 23, 27). The largest RCT of psilocybin for treatment-resistant MDD (27) incorporated an intermediate 10-mg dose in addition to the 25-mg treatment dose and 1-mg low-dose comparator, which holds potential promise as an ostensibly psychoactive dose that may improve blinding but also exert minimal or less prominent therapeutic effects. However, the 10-mg dose failed to differentiate from both the 25-mg and 1-mg groups on the primary outcome, and blinding integrity was not

assessed. Except for an RCT employing delayed treatment (13), all have examined comparator drugs and doses in the context of the same PST conditions between arms. Of these conditions, active placebos are theoretically the most rigorous comparator, but blinding psilocybin with diphenhydramine (21) or niacin (22, 24) has been unsuccessful. Additionally, all but one study have compared psilocybin to largely inactive treatment conditions, with the occasional exception of evidence-based psychotherapeutic techniques in the comparator arm as part of the PST package (19–21). A notable exception is the 2021 RCT comparing psilocybin to escitalopram, the only RCT to compare psilocybin to an active treatment (14). In summary, comparator conditions in existing RCTs have likely resulted in inflated efficacy estimates (due to unblinding), and there are not yet enough data to assess comparative efficacy relative to existing psychiatric treatments.

A frequently less well-considered factor in assessing integrity of clinical trial findings is expectancy effects. Expectancy for therapeutic effects has been most extensively

Psychological Support	N Randomized or Enrolled	Duration of Follow-Up	N Completed Study	Blinding Assessment and Success	Summary of Results
Individual therapy; participants each assigned a study therapist and psychiatrist; prep: 2-hr session the day before each dosing session; dosing: therapist and psychiatrist present for 6 hours; music and eyeshades; integration: two 1-hour sessions 1 day and 1 week after each dosing session	N=22 (13 female, 6 male), ages 20–61, mean age, 42.79 years	16 weeks	N=19 completed one dosing session, N=15 completed both dosing sessions	After placebo, 15 of 19 (78.9%) correctly guessed placebo; after psilocybin, 12 of 15 (80%) correctly guessed the drug and dose	Significant effect of time, but no significant time-by-drug interaction, on primary outcome (HAM-D) as well as secondary outcomes (HAM-A and QIDS-SR)
Individual therapy; participants each assigned a study therapist and physician; prep: two sessions, 1 week apart; second session ended with either visual healing or body scan meditation; dosing: reclining on couch and either watching visual healing versus eyeshades/music (randomized in first session; participant choice in second session); integration: 3 sessions after each dose, the first the day after dosing, the other two once weekly	N=20 (12 female, 8 male); mean age, 46.9 years in visual healing, 51.0 years in standard dosing setting	14 weeks	N=20 completed first dosing session, N=19 completed both dosing sessions and full study	N/A	After first dosing session, 1 participant relapsed into alcohol use and required inpatient treatment; a majority of participants agreed or strongly agreed that visual healing helped them feel relaxed and prepared for the psychedelic session and to feel more connected to nature; alcohol use decreased on average for all participants, with no significant differences between visual healing versus standard dosing procedure groups; peak increase in blood pressure following psilocybin dosing was significantly less (both systolic and diastolic) for those randomized to visual healing versus standard dosing procedures

studied in psychotherapy (44), but is also well known in the context of antidepressant medication treatment (45) in the form of the placebo effect (46). This is a very pertinent factor in the case of psilocybin with PST due to widespread positive media coverage, which can influence pretreatment expectations for potential benefit. In addition, the psychedelic experience itself may have an effect on shaping, reinforcing, or altering pretreatment expectations over the course of treatment (47). For example, it is possible that previously observed relationships between psilocybin-induced “mystical experience” and acute therapeutic benefits (13, 19, 23, 24, 30, 48, 49) may wholly or in part reflect a synergistic interaction between pretreatment expectations and subjective drug effects. This could result in a large-magnitude combination of true therapeutic effects bolstered by the actualization of expectations for improvement, that is, placebo effects. Despite the possibility of confounding effects, no published trials have assessed or reported standardized measures of pretreatment expectancies and relationships with therapeutic benefits.

An imbalance in individual preferences for a given treatment when two or more active treatments are compared can also serve as a threat to internal validity. One study has actively compared psilocybin to another active treatment condition (escitalopram for MDD) (14). The authors reported that most participants expressed a preference for psilocybin over escitalopram, a factor that may have interacted with functional unblinding to potentially alter therapeutic effect size magnitudes in the study (50). It will be important to assess, report, and test effects of individual treatment preferences in future studies comparing psilocybin to one or more other active treatments.

Finally, prior participant recreational and/or therapeutic exposure to psilocybin or other psychedelics may also impact subjective and therapeutic responses to psilocybin administered in a clinical trial. Early trials were typically composed of participants with some prior self-reported exposure to psilocybin or other psychedelics, which may be secondary to participant self-selection or researcher selection as a strategy to attempt to reduce likelihood of challenging drug

experiences (22–24). To mitigate the possibility of carryover effects, many recent studies have employed minimum durations of time prior to enrollment during which participants must not have ingested psilocybin or other psychedelics, ranging from 1 year (21, 27, 29) to 5 years (18). Another recently employed strategy is to limit the number of lifetime uses of psilocybin or other psychedelic compounds to a discrete number of experiences (18, 21, 26). It remains unclear what duration of time without psilocybin or other psychedelic exposure is effective in mitigating potential carryover effects prior to clinical trial entry, or whether extent or degree of prior psychedelic or psilocybin use exerts any measurable effect on therapeutic outcomes. Regular standardized assessment of duration of use, type of drug, number of experiences, and time interval between experiences in clinical trial participants and examination of these variables in relation to therapeutic outcomes is recommended to help clarify this issue.

Factors Affecting Generalizability

Here, we address two issues that impact generalizability of findings: sample size and representativeness. Most published trials have utilized small samples, which is a major limitation of the evidence base. Notable exceptions are two large RCTs of psilocybin for MDD in each of which over 100 participants were randomized to one of two to three treatment arms. A phase 2 study of single-dose psilocybin for treatment-resistant MDD (27) is the largest trial at this time, randomizing 233 participants to one of three treatment conditions, resulting in 75–79 participants per arm. A second phase 2 study of single-dose psilocybin for MDD (18) had a slightly smaller sample size per arm, with 51 to 53 participants in each. The phase 2 trial of psilocybin for AUD (21) is the third largest, randomizing 46–49 individuals per arm. All other studies have utilized much smaller samples, with a mean sample size of ~24 participants and a standard deviation of 16. Compare this to the mean sample size of studies employing traditional antidepressants, reported in a meta-analysis to be 224 participants, with a standard deviation of 186 (51). The sample size in most psilocybin trials is more comparable to those of noninvasive brain stimulation studies, which have a mean of 22 participants per trial, with a standard deviation of 24 (52). Given that the effect size of psilocybin tends to be large, especially acutely, existing studies have been able to demonstrate statistical significance in small samples. However, a primary concern is that the likelihood of large differences between a study sample and the population is inversely proportional to the sample size (53). Thus, findings in smaller samples are less likely to generalize. Although small studies are critical to informing the design of larger trials, all findings derived from these studies should be considered preliminary.

Beyond sample size, the extent to which a study sample represents the larger population is also hindered by a lack of sociodemographic diversity. Of 19 psilocybin RCTs reporting ethnicity breakdown, the mean percentage of the sample

composed of non-Hispanic Caucasian participants was 83.1%, with a standard deviation of 14.6% and a range of 30%–95%. Thus, knowledge regarding efficacy of psilocybin for psychiatric conditions largely applies to non-Hispanic Caucasian individuals. This is a major limitation to generalizability given that prevalence rates and the chronicity and course of psychiatric disorders such as AUD and MDD may vary between non-Hispanic Caucasian individuals and members of underrepresented minority groups (54–56). Thus, a truly representative estimate of the efficacy of psilocybin with PST will require clinical trials with more diverse samples. A lack of diversity in clinical trials is an ongoing issue in biomedical research (57). However, it may be possible to use this rapidly burgeoning area to spearhead diversity and inclusion efforts. A notable related example is the second phase 3 trial of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder, in which about one-third of the sample identified as non-White (58).

Adverse Events and Risk-Benefit Profile

Psilocybin and other psychedelic compounds exert acute effects on the cardiovascular system, raising heart rate, blood pressure, and body temperature (59). These drugs are therefore contraindicated for individuals with cardiovascular conditions such as uncontrolled hypertension, cardiac arrhythmias, and serious cardiovascular disease (60). Due to this reliable effect, existing studies have excluded individuals with cardiovascular conditions (see Tables S1–S7 in the online supplement). Blood pressure and heart rate are also tracked throughout the dosing session, and sustained elevations of blood pressure necessitating medical intervention are rarely reported. It is clear, however, that psilocybin can precipitate serious cardiac events in vulnerable individuals (61), and the risk-benefit profile may be unfavorable for those with uncontrolled cardiovascular conditions or at high risk for cardiac events. Until controlled studies are undertaken (e.g., in patients suffering with comorbid MDD and cardiac disease) to establish safety guidelines and risk parameters, the administration of psilocybin in such individuals remains contraindicated. In contrast, one survey-based study indicated a potential favorable relationship between psychedelic use and markers of cardiovascular health in the general population (62), which suggests a possibly complex relationship between psilocybin and cardiovascular health that may warrant further study.

Microdosing may pose particular risks to cardiovascular health through chronic activation of the 5-HT_{2B} receptor, which can promote valvular heart disease (VHD) (63). Psilocybin binds with varying degrees of affinity to 5-HT receptors other than the 5-HT_{2A} receptor, including the 5-HT_{2B} receptor. If this occurs with sufficient frequency and intensity, cardiac 5-HT_{2B} receptor binding has been shown to promote VHD through stimulation of myofibroblast mitogenesis and extracellular matrix deposition, leading to thickened valve leaflets and possible myocardial

dysfunction, congestive heart failure, and sudden death (64). Although VHD has not yet been reported in individuals microdosing psilocybin or other psychedelics with typical modern protocols (e.g., a few times a week), there is some evidence that regular and potentially excessive use of MDMA (which operates via a different mechanism but also results in 5-HT_{2B} receptor activation) may result in VHD (65, 66). However, there are no reported cases of VHD with infrequently administered psilocybin as delivered in existing clinical trials. Thus, risk of VHD with currently adopted dosing procedures appears minimal. Further research is needed to assess the risk-benefit profile of psilocybin microdosing in regard to VHD.

Acutely and post-acutely (e.g., 1–2 days after administration), there are several adverse events frequently reported in existing studies (see Tables S1–S7 in the online supplement). These include transient hypertension, fatigue, headache, nausea/vomiting, physical discomfort, psychological distress, fear/anxiety, transient paranoid ideation, tearfulness, euphoria, and visual/perceptual alterations. The most commonly reported adverse events include headache, nausea, and fear/anxiety, all of which appear to increase in frequency and/or intensity with higher doses. Headache was identified quickly as a likely adverse event of psilocybin administration in healthy individuals (67), which has been replicated in clinical trials. The predominance of anxiety and nausea underlies the value of keeping rescue medications on hand (e.g., benzodiazepines for anxiety/panic, antiemetic medications), although transient fear/anxiety can often be managed by session therapists.

Less common but more concerning adverse events include paranoid, manic, or psychotic symptoms persisting beyond the typical window of consciousness alteration (5–6 hours). Although not yet reported in existing clinical trials, there are case reports describing this in individuals taking psilocybin mushrooms recreationally and manifesting severe first episodes of mania and/or psychosis (68–70). Such cases justify the common practice of excluding from psilocybin trials individuals with prior histories (or with histories in first-degree relatives) of bipolar or psychotic disorders. The potential for psilocybin to induce drastic and long-lasting negative mental health consequences clearly exists, but the relative likelihood of such an event occurring in the general population remains unknown.

Another possible risk is worsening of depression and mood, new-onset suicidal ideation and behavior, and potential aggravation of comorbid conditions during or following psilocybin administration. Such cases appear to be rare, but there are several concerning reports. The first was in the context of a 2016 trial examining psilocybin for anxiety/depression associated with a life-threatening cancer diagnosis (23). The supplement reports a death by suicide of a participant 11 days after the first dosing session with the low-dose comparator. This volunteer was discontinued from the study after insisting on leaving the session early, and the authors noted no behavioral impairment and no adverse

sequelae on follow-up that day and over subsequent days. The suicide was determined to be related neither to the study procedures nor to the psilocybin. More recent trials, such as the large, multisite phase 2b study of psilocybin for treatment-resistant MDD (27), reported higher rates of suicidal ideation and self-injury for the two active doses (10 mg and 25 mg) compared with the 1-mg comparator after dosing and up to 12 weeks after dosing (see Table S5 in the online supplement). The authors report that of the three participants demonstrating suicidal behavior after week 3, all had a prior history of suicidal behavior or nonsuicidal self-injury prior to the trial and did not demonstrate a treatment response at week 3. These observations remain concerning given that recent or current active suicidal ideation or behavior was an exclusionary criterion for enrollment, but it remains unclear as to the potential causal role of psilocybin in these behaviors and whether participant expectations for treatment response and potential unblinding to drug dose may have interacted with a poor therapeutic response to potentially promote these behaviors.

Additional cases of worsening mood leading to hospitalization have been reported in the aforementioned study and another MDD psilocybin study (27, 29), and a pilot study in body dysmorphic disorder (36) reported one incident of mood lability (tearfulness, sadness) more than 1 week after dosing. One participant from a 2014 study of psilocybin for tobacco dependence reported reliving traumatic experiences from childhood during her first dosing session, for which she was referred for counseling (20). From a trial examining psilocybin with group PST for treatment of demoralization in older long-term AIDS survivors (39), there were two unexpected drug reactions occurring after acute effects had subsided. One was a posttraumatic flashback occurring 2 days after dosing in which a participant vividly reexperienced a sexual assault. The second was severe anxiety in a participant occurring 10 days after dosing, which resulted in subsequent relapse into methamphetamine use and withdrawal from the study. In aggregate, these rare but significant adverse events highlight the need for meticulous safeguards for participant well-being during and after dosing as well as additional research to determine why such events occur, whether they can be predicted or vulnerable individuals identified, and potential methods to minimize their likelihood.

Finally, we note the possibility of lingering or “flashback” perceptual disturbances following psilocybin administration, which can fall under the DSM-5 diagnosis of hallucinogen persisting perception disorder (HPPD) (71) when disturbances cause significant distress or impairment. The etiology of this condition is poorly understood, but it has been suggested to be more common following LSD or phencyclidine administration compared with other compounds (71). Cases of “flashback” perceptual phenomena—reexperiencing perceptual disturbances associated with psilocybin administration unexpectedly after acute drug effects have subsided—have been reported in some trials,

including psilocybin for body dysmorphic disorder (in one of 12 participants) (36) and MDD (in one of 26 participants, and in three of 52 participants) (18, 41). Such “flashback” phenomena were also reported to occur in about 10% of healthy individuals participating in modern psychedelic drug administration studies (72). However, the development of HPPD (“flashbacks” associated with distress or impairment) has not been reported in modern psilocybin trials, but it remains unclear as to the extent to which this was tracked with fidelity or queried across studies.

Psychological Treatment Components

All existing studies have incorporated PST before, during, and after dosing, which is informed both by safety considerations and by early work suggesting the importance of proper preparation and support before and during dosing to mitigate adverse outcomes (15). The majority of existing studies have utilized a focused psychological support framework (see the online supplement for a detailed description) that emphasizes, at minimum, psychoeducation and rapport building in the preparation phase (prior to dosing); nondirective, supportive therapeutic presence during the entirety of the dosing session; and one or more integration or debriefing sessions after dosing to provide the participant an opportunity to discuss, process, and make meaning of their subjective experience (11). Of 21 reviewed trials, 17 utilized a predominantly psychological support–focused model (of which one study used an additional nature video manipulation during the first dosing session). Several of these trials refer to the psychological component as being informed by theoretical models such as a medication-assisted psychotherapy (incorporating elements of existential, cognitive-behavioral, and psychodynamic therapy) (24); an accept-connect-embody model (73) informed by theories of psychological flexibility (14); a perceptual control theory model (74) in which perceptual experiences promoted by psilocybin are theorized to facilitate greater control and optimization of mental health–relevant psychological variables (27, 28, 36); and an acceptance and commitment therapy–informed model (75) adapted for psychedelic administration (29). The other four trials have incorporated PST approaches adapted from evidence-based therapy models designed and validated outside the context of psychedelic administration, including cognitive-behavioral therapy (CBT) for smoking cessation (20, 76), motivational enhancement therapy (MET) for AUD (19), a mix of CBT and MET approaches designed for combination with psilocybin (77) for treatment of AUD (21), and a brief supportive-expressive group therapy treatment designed as a palliative care–focused intervention and applied to the treatment of demoralization in older male survivors of AIDS (39). These four trials have all incorporated psychological techniques from these evidence-based approaches before and after (but not during) psilocybin administration.

Regarding individual versus group modality, 18 of 21 trials have utilized only individual PST (with one to two therapists per patient), and three have incorporated group PST as part

of the preparation and/or integration/debriefing phases (30, 31, 39). An entirely group-based administration session was also implemented in one trial, with participants dosed in the same large room but separated by semiprivate bays with communal music broadcast over loudspeakers (30). Although a group administration model provides an enticing option to potentially reduce personnel and provider costs, the ratio utilized in the study still employed a 1:1 participant-to-provider ratio. Two other studies have also conducted group administration, but with participants dosed simultaneously in separate rooms with at least one dedicated provider (28, 31). A notable inferential limitation of the existing evidence base is the inability to disentangle effects of psilocybin from the interaction of psilocybin with PST components, which would require more complex factorial designs with additional comparators (e.g., psilocybin without PST) that may not be safe or feasible (11). One pilot study manipulated a setting variable during dosing sessions in the context of similar drug and dose administration (nature-themed video watching vs. standard dosing procedures) but was not powered to detect differences in clinical outcomes (33). However, the most proximal advance regarding potential synergy of psilocybin with PST could be offered by trials investigating the same dose of psilocybin in the context of two different PST protocols, with an “active” PST (such as CBT) compared to an “inactive” PST (focused psychological support) to determine the magnitude of incremental benefit acutely and long-term.

Predictors of Therapeutic Response

Knowledge of pretreatment variables predicting favorable therapeutic responses to psilocybin with PST remains scarce. Some studies have observed relationships between the quality of the acute subjective experience and subsequent therapeutic response (13, 19, 23, 24, 30, 48, 49). Participants who experience a greater degree of mystical experience (feelings of unity, sacredness, noesis, positive mood, transcendence of time and space, and ineffability) (78) under the effects of psilocybin report more dramatic acute improvements in symptoms of AUD (19), anxiety/depression associated with a cancer diagnosis (23, 24, 30), tobacco dependence (48), and MDD (13, 49). However, these relationships are not consistently observed (26, 41) and are not always assessed or reported, and long-term follow-up data generally indicate an absence of relationship between quality of subjective experience and long-term clinical improvements (25, 41). Interestingly, one study observed that greater degree of mystical experience predicted more favorable depression symptom change following inactive placebo but not psilocybin (29). Thus, it remains unclear whether quality of subjective experience can serve as a robust or reliable predictor of subsequent therapeutic improvements, whether this may vary by clinical indication, whether such relationships are limited to acute outcomes only, and whether such relationships index drug effects, placebo effects, or a combination of the two. Finally, it is worth noting that two

studies have reported that natural language processing measures obtained from a baseline autobiographical memory interview (79) or psychological support sessions provided the day after dosing (80), combined with machine learning approaches, demonstrated initial evidence of capacity to distinguish later treatment response versus non-response in treatment-resistant MDD. Additional research is needed to replicate initial findings, but the incremental value of an accurate predictive marker derived from natural language prior to dosing (79) would substantially exceed that of one derived from after dosing (80).

DISCUSSION

Mechanism(s) of Change

Despite the challenges inherent to conducting this research, clinical trials have produced a substantial evidence base for psilocybin with PST. The current evidence base indicates that psilocybin with PST may exert durable therapeutic effects for a subset of individuals with various psychiatric disorders, with the strongest evidence for MDD (three double-blind RCTs with positive signals spanning a range of severities, but with no assessment of blinding integrity). Conclusions must be tempered, however, by the potential threats to internal and external validity noted above. Preliminary evidence of efficacy across multiple diagnoses and outcome domains suggests that 1) the mechanism of action generalizes to various facets of mood, emotion, and cognition across a range of diagnoses; and/or 2) there are several mechanisms of action spanning levels of analysis (e.g., molecular, circuit-level, psychological), with possible time-varying contributions. There is insufficient evidence to clearly arbitrate among the many proposed mechanisms of action (81), but here we adopt a potentially useful heuristic (not novel, but adapted from existing models of psychedelic drug action [82, 83]) for integrating existing theories and conceptualizing methods to sharpen understanding of underlying mechanisms: disruption and remodeling.

The disruption and remodeling perspective emphasizes two distinct but possibly related temporal facets of psilocybin and psychedelics more broadly: the acute disruption of typical states of consciousness and mental, perceptual, and neurobiological functions (8), and the longer-term post-acute shifts marked by more subtle psychological and neurobiological changes as well as changes in gene expression (84), cellular markers of neuroplasticity (85), cognitive and emotional function (86, 87), and circuit organization and dynamics (87, 88). In the acute phase, human and animal mechanistic studies clearly demonstrate that psilocybin and other psychedelics disrupt stereotypic patterns of circuitry dynamics, postulated to occur through thalamocortical gating (8), altered balance of top-down predictions and bottom-up sensory processing (89, 90), and/or disrupted organization of cortical networks (91). Acute effects appear largely dependent on functionally selective 5-HT_{2A} agonism, as antagonizing 5-HT_{2A} receptors eliminates the

vast majority of subjective psychedelic effects (8). However, even with 5-HT_{2A} antagonism, subtle changes in human brain function (92) are still detectable, behavioral and plastogenic effects of psilocybin persist in animals (85, 93), and therapeutic effects may also continue to manifest (94). This suggests that psilocybin's effects may not be fully mediated by the 5-HT_{2A} receptor, but the profound disruption of circuit functional organization and normal cognitive, emotional, and perceptual functions largely depend on this receptor target. Of relevance to this disruption phase are the behavioral catalyst model, which proposes that psychedelics catalyze the PST component to overcome blocks to a successful psychotherapeutic resolution, and other models pertaining to how the quality of the acute psychedelic experience (e.g., awe, mystical experience, altered perception of the self, corrective emotional experiences, and experiences promoting shifts in personal and metaphysical beliefs) may promote long-term positive changes (81). The acute neurobiological disruption effect has also been proposed to facilitate the disentanglement of brain networks from maladaptive failure modes (82) that may characterize diverse forms of psychopathology (83).

The remodeling phase is emphasized most heavily by the psychoplastogen model and the critical-period-reopening models of psychedelic action. The former emphasizes the long-term upregulation of neuronal plasticity, evidenced by increases in dendritic arbor complexity, spine size and density, and synapse formation that onset rapidly and persist beyond the window of acute subjective effects (85, 95). The latter emphasizes the potential for psychedelic-induced "metaplasticity"—that is, the degree to which neuroplasticity can adaptively shift versus general increases in plasticity also observed with stimulant drugs that do not demonstrate psychedelic-like therapeutic effects—to facilitate reopening of a critical period for learning and/or experience to influence behavior, first demonstrated with social reward learning (84). Psychedelic plasticity-promoting effects have been variably demonstrated across studies to depend on intracellular 5-HT_{2A} binding (96) and allosteric potentiation of brain-derived neurotrophic factor (BDNF) binding to tropomyosin receptor kinase B (TrkB) (97). Nonpsychedelic psychoplastogen compounds have been engineered and shown to exert favorable behavioral effects in animal models (5, 98, 99), and such compounds are already being developed commercially for investigation in humans. Other theories of therapeutic mechanisms also emphasize the remodeling period, including post-acute enhancement of psychological (100) and cognitive flexibility (86), feelings of connectedness (101), restoration of personal meaning (102), and potential anti-inflammatory effects (103, 104).

Of key importance from the disruption and remodeling perspective is the distinction between acute and long-term effects of psilocybin, and dissociating unique therapeutic contributions from each may aid in a better understanding of underlying mechanisms. Intuitively, the rapid-onset acute therapeutic effects of psilocybin, manifesting in the span of

hours, are likely largely mediated by processes occurring in the disruption phase. This is consistent with observations that quality of subjective experience predicts psilocybin therapeutic outcomes at acute endpoints (13, 19, 23, 24, 30, 48, 49) but not long-term follow-up (25, 41). In contrast, more distal outcomes are likely more heavily influenced by processes in the remodeling phase, which is consistent with evidence in a mouse model that psilocybin-promoted increases in dendritic spine formation last for up to a month after dosing and do not completely depend on 5-HT_{2A} receptor activation, which is critical for acute subjective effects in humans (85). Efforts are currently under way to dissociate effects in these phases, largely focused on eliminating the subjective psychedelic experience (or conscious awareness of it through anesthesia, as recently shown with ketamine [105]) via nonpsychedelic psychoplastogenic drugs, or testing whether psilocybin administered with a 5-HT_{2A} antagonist to block the psychedelic experience will exert therapeutic properties similar to psilocybin plus placebo (106). More distally, if commercially developed psychoplastogenic compounds accumulate sufficient safety data to warrant human testing, the direct comparison of psilocybin versus a nonpsychedelic psychoplastogen with similar plasticity-promoting properties in the remodeling period will be a critical test of the relative contribution of the disruption effect, which appears to be tightly linked to conscious psychedelic experience. These efforts will provide initial informative data to dissociate the relative contributions of the two components.

Here, we propose that bidirectional manipulation of the proposed mechanistic processes in both phases (disruption and remodeling) will provide the most comprehensive test of each component's contribution—specifically, interrogating in both phases enhancement of hypothesized therapeutically relevant processes as well as removal or attenuation of these processes. Current efforts are largely aimed at removing the subjective changes in consciousness (or awareness of them) and the acute disruptive effects of psychedelics and testing whether longer-term effects in the remodeling phase demonstrate comparable therapeutic effects. Additional efforts to enhance processes in the disruption phase might include in-session psychological, physiological, or immersive virtual reality approaches during dosing to maximize behavioral (e.g., speech patterns), psychological (e.g., mystical experience), or neurobiological markers (EEG readouts) of circuit disruption; or neuromodulatory interventions applied before or during acute effects to condition circuitry for maximal therapeutic disruption. Such efforts depend on development of an accurate readout of acute effects that predict long-term therapeutic benefits.

In contrast, potentiation of processes in the remodeling phase could include delivery of enhanced forms of psychotherapy or cognitive/affective training (107) to promote adaptive learning in concert with putative enhanced neuroplasticity, or the delivery of therapeutic neuromodulation to synergize with psilocybin-induced remodeling potential.

Knockout or attenuation of psilocybin-induced adaptive processes in the remodeling phase (e.g., plasticity) remains methodologically elusive but may one day be actualized through better knowledge of processes mediating this effect and/or engineering and testing of psychedelic compounds lacking plastogenic properties. Although currently rudimentary, our developing understanding of mechanisms will benefit from consideration of processes in each of these temporal phases and careful manipulation of hypothesized variables in each to dissociate relative contributions.

RECOMMENDATIONS

Establish Optimal Dosing

Little is known regarding optimal dosing of psilocybin, which in some studies is weight based and in others fixed. Initial evidence indicates that weight-adjusted versus fixed dosing does not substantially affect the subjective effects (108, 109), but there are no studies examining how dosing adjustment may impact short- and long-term clinical outcomes. Whether dose escalation versus single or multiple high-dose administrations impacts subjective experience, number and severity of adverse events, and long-term therapeutic outcomes is also unclear. Moreover, common dosing tiers and maximal tolerated doses have not yet been established in humans (110). Therefore, we recommend that additional studies be conducted to address dose optimization, with a focus on identification of best dosing practices and relevant dosing considerations that may maximize therapeutic effects and minimize adverse events. Other important questions include the potential efficacy of microdosing psilocybin versus the current high-dose, episodic administration model. Initial work in healthy individuals demonstrates subtle effects on subjective experience (37, 111), language production (38), and EEG rhythms (37) that may be attributable to participant unblinding, but no effects on emotion processing, anxiety, or depression (112). Future efforts should determine whether microdosing exerts a therapeutic effect in clinical populations.

Assess Treatment Expectancy and Improve Blinding

Future studies should assess, with validated instruments, participant expectations for therapeutic benefit prior to treatment. Blinding psychedelics is a perpetual challenge (43), and there is currently no widely accepted solution. Inactive placebos, niacin, diphenhydramine, and very low doses of psilocybin (e.g., 1 mg) all seem ineffective in blinding, but potential insights may be offered from dose comparison studies. In a large phase 2b study in treatment-resistant MDD (27), 10-mg and 1-mg doses exerted roughly equivalent efficacy and response and remission rates, suggesting similar lack of efficacy compared with the 25-mg dose. The key comparison of differences in 25-mg versus 10-mg doses on clinical outcomes was not reported due to the hierarchical testing procedure, but response and remission rates suggest that 25 mg may be clinically superior to 10 mg.

If so, an informative question is whether 25-mg and 10-mg doses can be accurately distinguished by participants and providers. Due to a lack of reporting on blinding effectiveness in this and other studies utilizing similar dosing (12, 26), this question remains unanswered. Because a dose of 15–16 mg was found to be efficacious in mild to moderate MDD (26) and a 10-mg dose had minimal therapeutic effects in treatment-resistant MDD (40), available data suggest that a dose of ~10 mg may be effective in maintaining the blind but also lack substantial efficacy. This remains to be empirically validated.

As this could be better addressed with additional assessment and reporting, we recommend that future research routinely assess and report effectiveness of blinding procedures in participants and providers. This provides critical information for judging the accuracy and strength of the evidence. Additional methods of ensuring effective blinding should also be tested and pursued. Potential options include comparison of psilocybin and a psychoactive substance with ostensibly limited clinical efficacy and a different mechanism of action (e.g., tetrahydrocannabinol, amphetamines, benzodiazepines), use of a psychoactive comparator with clinical efficacy but with a targeted manipulation to block therapeutic but not subjective effects (e.g., ketamine combined with naltrexone [113]), enrolling individuals who are psilocybin naive, and/or incorporation of augmented (114) or virtual reality (115) procedures to mask or mimic some perceptual effects of psychedelics.

Increase Sample Size and Diversity for Enhanced Generalizability

Most studies have administered psilocybin to carefully screened, culturally and clinically homogeneous small samples, primarily highly educated Caucasian individuals. Symptom severity and treatment resistance across studies with the same inclusion diagnosis also vary quite broadly (e.g., treatment-resistant MDD vs. mild to moderate MDD), which renders comparison of effects across studies and in relation to other second-line treatments difficult. Studies have been conducted with small samples, primarily owing to lack of sufficient funding. However, larger studies with more diverse patient populations are needed to enhance the evidence base. With increasing commercial interest (116) in psychedelics and slowly shifting attitudes toward funding research on their therapeutic applications, studies with large and representative patient samples are now a realizable possibility (27).

Therefore, future studies in indications with existing positive pilot studies should aim to recruit larger, more diverse patient samples. It is also helpful, where appropriate, to adopt inclusion criteria on symptom severity and treatment resistance comparable to those of prior trials for other evidence-based, second-line treatments to facilitate comparison across studies. Given the financial cost of this treatment and concerns regarding scalability, it is unlikely that psilocybin with PST would be utilized as a first-line

treatment approach in most clinical settings. Thus, a focus on populations that have failed to benefit from existing first-line treatments will be of most proximal value.

Investigate Moderators and Mediators of Therapeutic Response

Investigation of baseline moderators and mediators of treatment response should be undertaken. There is currently a dearth of evidence in this area. Across all indications at this time, 579 individuals have received at least one psilocybin dose in a modern RCT (Table 1). A study sufficiently powered to detect a moderation effect of moderate effect size (i.e., between-arm difference in correlation coefficients of 0.3 between a continuous moderator variable and the clinical outcome) requires ~160 individuals in each of the two treatment arms (117, 118), which is far larger than any psilocybin trial conducted to date. However, future studies should undertake exploratory analyses to test candidate moderators and mediators of clinical response, which can be reported for hypothesis generation. Results can be reported with descriptive effect sizes rather than statistical significance tests. These analyses will inform the design of adequately powered studies to explicitly test candidate moderator or mediator variables. They will also inform initial efforts toward designing multivariate machine learning approaches that aim to predict treatment response at the individual patient level. These findings will address the more clinically informative questions regarding “for whom,” “when,” and “how” a treatment should be administered.

Utilize Additional Comparators to Dismantle Effects

Psilocybin trials have thus far always administered the drug with PST. Although necessary for safety, it is impossible to dissociate the therapeutic effects of the drug itself from those stemming from or interacting with the PST component without additional comparators. A lack of standardization of PST procedures across studies also renders comparison of effects between studies difficult. To address these issues, future studies should incorporate, when possible, comparator conditions that facilitate dissociation of these two components’ therapeutic effects. Although administration of psilocybin without PST poses safety concerns (15), the dismantling of therapeutic effects related to number and type of preparation and integration sessions may inform initial modifications of the treatment paradigm to better facilitate delivery at scale.

Other considerations include incorporation of evidence-based treatment approaches (e.g., CBT or MET) into the therapeutic regimen (119). This has been adopted in several studies (19–21, 39), but without comparators to facilitate inference on effects of psilocybin in the absence of evidence-based PST approaches. Such comparisons will be critical to understanding the active elements of this hybrid approach, which could vary by disorder or population. Lastly, PST frameworks utilized in future studies should be manualized and made available to the lay and scientific communities to

facilitate consistency, model adherence, and comparison across studies.

Investigate Effects of Concomitant Medications

Little is known regarding how concomitant psychiatric medications (e.g., antidepressants, sedative-hypnotics, mood stabilizers, stimulants) may impact the efficacy of psilocybin with PST. An initial small study in individuals with treatment-resistant MDD who were maintained on SSRI monotherapy suggests a roughly equivalent safety, therapeutic, and subjective experience profile (28). Additionally, a study in healthy individuals treated with an SSRI (escitalopram) over a short lead-in period demonstrated that the combination evoked roughly equivalent positive mood enhancement and transpersonal aspects of the psychedelic experience while attenuating cardiovascular stimulation and adverse drug effects (120). However, additional survey-based research suggests an overall attenuation of psilocybin mushroom subjective effects in those currently taking antidepressants (121). Further studies are needed to address this question, particularly large studies of individuals maintained on antidepressant medication and examining antidepressant use as a moderator of therapeutic effects (or as a stratification variable). This will provide much-needed evidence to assess the safety and efficacy of psilocybin administration concomitantly with regular antidepressant use, which is likely to be a critical consideration if this treatment approach moves toward widespread dissemination.

Assess and Control for Prior Psychedelic Use

Several studies have utilized samples with some or an extensive history of prior psychedelic use. Studies have not investigated whether presence or degree of past psychedelic use impacted clinical outcomes, but this is an important factor that we recommend be assessed, controlled, or explicitly tested in future studies. It is reasonable to hypothesize that an extensive prior history of psilocybin or other psychedelic use may differentially impact clinical response in such studies, which remains to be investigated.

Conduct Comparative Efficacy Trials

As findings from large double-blind RCTs of psilocybin for various clinical indications continue to be reported, we recommend that research focus on conducting comparative efficacy trials of active treatments. One comparative efficacy trial has already been reported (14), but the results did not show a significant difference between psilocybin and escitalopram on the primary outcome, likely due to a lack of statistical power (122). Such studies will be informative for establishing whether psilocybin with PST is superior to existing treatment modalities, for investigating differential baseline prediction of treatment response, and for identifying common and differential mechanisms of action (88). Prediction of treatment response moves the field toward precision medicine, where patients are assigned to a best-suited treatment modality rather than those that may be a poor fit for their individual neurobiology. Knowledge of

mechanisms informs development of enhanced and novel treatment modalities to target a specific or common mechanism of change more directly, thereby enhancing the repertoire of available therapeutic tools.

Provide Accurate Education to Interested Patients

The personal use of psilocybin mushrooms in pursuit of health benefits is growing in popularity (123), and efforts to decriminalize natural psychedelic products in various parts of the United States enhance availability for interested consumers (124). For clinicians fielding questions from patients considering the use of psilocybin mushrooms, it is of utmost importance to emphasize the key distinction in purity and stability between the synthetic, highly pure psilocybin used in all current clinical trials from dried or fresh psilocybin mushrooms, which have highly variable concentrations of psilocybin, psilocin, and accessory alkaloids (baeocystin and norbaeocystin). Alkaloid levels furthermore vary with passage of time and the conditions and methods used for processing and storage (125). Thus, patients should be counseled that use of natural mushroom products should not be considered as a substitute for the precise dosing and purity offered by synthetic pharmaceutical-grade psilocybin, and it is not currently possible to draw parallel conclusions between the two regarding safety and efficacy. In such cases, clinicians should attempt to refer the patient to a trial approved by the U.S. Food and Drug Administration (FDA), when possible.

CONCLUSIONS

There has been a surge of scientific evidence and public interest in psilocybin with PST for the treatment of mental health disorders over the past quarter century. At present, psilocybin with PST is not approved by the FDA for the treatment of any medical condition. We conclude that the current evidence base is not yet sufficiently developed to warrant use of psilocybin with PST as a psychiatric treatment. The evidence is most promising for MDD (N=388 dosed in three double-blind RCTs, all with positive signals spanning mild to moderate MDD to treatment-resistant MDD).

We recommend that research continue to be conducted, in line with the aforementioned recommendations, to establish clinical efficacy of psilocybin with PST in large, well-characterized, generalizable samples with validated clinical outcome measures, using additional secondary measures to inform on mechanisms of action and baseline moderators of treatment response. Comparative efficacy studies placing psilocybin head-to-head with other established treatments will better inform on its relative role in treatment sequencing. Significant remaining barriers include blinding, establishment and adoption of evidence-based dosing procedures, reduction of expectancy effects from self-selected samples with strong treatment preferences, and validation of patient safety considerations and contraindicated medications or treatments. As the quality of accumulating evidence

continues to improve, psilocybin with PST may one day reach the cusp of FDA approval and become adopted as a legitimate psychiatric treatment.

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QUESTIONNAIRE

C10(26) Part 1 of 3

Psilocybin: From Psychiatric Pariah to Perceived Panacea

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- **Some questions may have more than one correct answer;** in which case you must mark **all** the correct answers.

Question 1: Psilocybin is an indolylalkylamine psychedelic prodrug produced by more than 200 species of fungi distributed across all continents (except Antarctica).

- A. TRUE
- B. FALSE

Question 2: Psilocybin ingestion induces transient and highly variable effects across all of the following domains, **EXCEPT**

- A. Cognitive
- B. Affective
- C. Physical
- D. Perceptual

Question 3: The time course of subjective effects is?

- A. 30-45 min
- B. 4–6 hours
- C. 6-8 hours
- D. 10-30 min

Question 4: Reported effects include acute changes in which of the following? Select all three correct options.

- A. Emotional processing
- B. Alterations in sense of self
- C. Changes in sensory perception and shifts in attention, working memory, and executive function
- D. Perceived physical strength

Question 5: During the first phase (preparation), the patient meets with the therapist(s) for

- A. Reduced dose first psilocybin administration to test for hypersensitivity
- B. Relaxation with headphones and eyeshades
- C. Psychoeducation and informed consent

Question 6: In the _____ phase (dosing), psilocybin is administered, and the patient is encouraged to rest in a comfortable position, wear headphones and eyeshades, and focus their attention inward.

- A. First
- B. Second
- C. Third
- D. Final

Question 7: Sessions typically commence in the morning to accommodate the full duration of psilocybin's effects, with a peak onset of effects at _____ minutes after ingestion.

- A. 10-20
- B. 20-30
- C. 40-60
- D. 60–90

Question 8: In the _____ phase (integration), the patient meets with the therapist(s) for a debriefing to discuss the experience, adverse effects, and/or safety issues.

- A. First
- B. Second
- C. Third

Question 9: Therapist(s) may offer additional guidance to aid the participant in coming to a subjective sense of insight regarding the experience. The process typically occurs over the course of _____, depending on the number of planned dosing sessions.

- A. 1-4 days
- B. 1–4 weeks
- C. 4-6 weeks
- D. 2-3 days

Question 10: Several studies have reported therapeutic benefits of psilocybin with psychological support/therapy (PST) in which of the following? Select all three correct options.

- A. Major depressive disorder (MDD)
- B. Alcohol and tobacco use disorders
- C. Childhood trauma
- D. Anxiety and depression associated with life-threatening illness

Question 11: Studies demonstrated a statistically superior effect of a single psilocybin dose (_____ mg) with PST versus inactive placebo, low-dose psilocybin (_____mg), or 100 mg niacin (active placebo) on the primary outcome measure.

- A. 15–25; 1
- B. 1; 15-25
- C. 5-10; 2
- D. 15-25; 5

Question 12: An open-label trial of 25 mg psilocybin in participants with treatment-resistant MDD maintained on selective serotonin reuptake inhibitor (SSRI) monotherapy demonstrated a safety and efficacy profile very similar to that in patients who were tapered off antidepressants.

- A. TRUE
- B. FALSE

Question 13: Alcohol use disorder (AUD) demonstrated a statistically superior reduction for psilocybin versus diphenhydramine on monthly percentage of heavy drinking days over the ____ weeks following the first study drug administration.

- A. 23
- B. 12
- C. 8
- D. 32

Question 14: Initial positive findings have also been demonstrated in which of the following clinical indications in the context of single-arm, open-label trials? Select all correct options.

- A. Obsessive-compulsive disorder
- B. Emotional dependence
- C. Older long-term male survivors of AIDS suffering from demoralisation
- D. Anorexia nervosa and body dysmorphic disorder

Question 15: In 11 of 21 reviewed trials, dosing was based on body weight, with doses ranging from ____ mg/70 kg (a low/inactive comparator dose) to ____ mg/70 kg (a very high dose administered in a dose-ascending design).

- A. 2; 25
- B. 1; 40
- C. 4; 40
- D. 5; 50

THE END

QUESTIONNAIRE

C10(26) Part 2 of 3

Psilocybin: From Psychiatric Pariah to Perceived Panacea

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- Some questions may have more than one correct answer; in which case you must mark **all** the correct answers.

Question 1: Fixed dosing, with _____ mg was generally used as the active dose in single-dosing-session studies.

- A. 25
- B. 12
- C. 40
- D. 30

Question 2: Effective weight-based doses in MDD appear to range from _____ mg/70 kg for mild to moderate MDD to _____ mg/70 kg for moderate to severe MDD.

- A. 30; 15
- B. 25; 30
- C. 15; 30
- D. 15; 40

Question 3: Existing randomized controlled trials have only variably reported on benefits beyond acute clinical endpoints. Across indications, acute clinical endpoints have ranged from 1 day to around 12 weeks, with longer-term follow-up outcomes assessed over several months or 1 or more years.

- A. TRUE
- B. FALSE

Question 4: One of the most prominent challenges to internal validity in trials of psychedelic compounds is effectively maintaining blinding.

- A. TRUE
- B. FALSE

Question 5: The psychedelic experience itself may have an effect on shaping, reinforcing, or altering pretreatment expectations over the course of treatment. To mitigate the possibility of carryover effects, many recent studies have employed minimum durations of time prior to enrolment during which participants must not have ingested psilocybin or other psychedelics, ranging from _____ to _____.

- A. 1 month; 5 months
- B. 1 year; 5 years
- C. 6 months; 1 year
- D. 1 week; 5 months

Question 6: Two issues that impact generalisability of findings are?

- A. Instrument reliability
- B. Chosen significance threshold
- C. Sample size
- D. Representativeness

Question 7: Psilocybin and other psychedelic compounds exert acute effects on the cardiovascular system, raising heart rate, blood pressure, and body temperature. Blood pressure and heart rate are also tracked throughout the dosing session, and sustained elevations of _____ necessitating medical intervention are rarely reported.

- A. Heart rate
- B. Breathing rate
- C. Body temperature
- D. Blood pressure

Question 8: These drugs are contraindicated for individuals with cardiovascular conditions such as which of the following? Select all correct options.

- A. Uncontrolled hypertension
- B. Cardiac arrhythmias
- C. Diabetes
- D. Serious cardiovascular disease

Question 9: Microdosing may pose particular risks to cardiovascular health through chronic activation of the 5-HT_{2B} receptor, which can promote which of the following?

- A. Ventricular arrhythmias
- B. Hypertrophic cardiomyopathy
- C. Valvular heart disease (VHD)
- D. Diabetes

Question 10: Acutely and post-acutely (e.g., 1–2 days after administration), there are several adverse events frequently reported in existing studies. These include all of the following, **EXCEPT**?

- A. Transient hypertension
- B. Fatigue, headache, nausea / vomiting
- C. Psychological distress, fear / anxiety, tearfulness, or euphoria
- D. Hyperactivity

Question 11: The predominance of _____ and _____ underlies the value of keeping rescue medications on hand.

- A. Anxiety; nausea
- B. Hallucinations; depression
- C. Hypothermia; nausea
- D. Hyperthermia; agitation

Question 12: Less common but more concerning adverse events include paranoid, manic, or psychotic symptoms persisting beyond the typical window of consciousness alteration (_____ hours).

- A. 1-2
- B. 2-4
- C. 5-6
- D. 6-8

Question 13: Although not yet reported in existing clinical trials, there are case reports describing severe first episodes of mania and /or psychosis in individuals taking psilocybin recreationally. Such cases justify the common practice of excluding from psilocybin trials individuals with which of the following? Select **BOTH** correct options.

- A. Prior history of bipolar or psychotic disorders
- B. Histories in first-degree relatives of bipolar or psychotic disorder
- C. History of depression
- D. PTSD

Question 14: Other possible risks during or following psilocybin administration include which of the following? Select all three correct options.

- A. Worsening of depression and mood
- B. New-onset suicidal ideation and behaviour
- C. Permanent cognitive impairment
- D. Potential aggravation of comorbid conditions

Question 15: “Flashback” phenomena were reported to occur in about _____% of healthy individuals participating in modern psychedelic drug administration studies.

- A. 20
- B. 10
- C. 30
- D. 50

THE END

QUESTIONNAIRE

C10(26) Part 3 of 3

Psilocybin: From Psychiatric Pariah to Perceived Panacea

INSTRUCTIONS

- Read through the article and answer the multiple-choice questions provided below.
- **Some questions may have more than one correct answer;** in which case you must mark **all** the correct answers.

Question 1: Participants who experience a greater degree of _____ under the effects of psilocybin report more dramatic acute improvements in symptoms of AUD, anxiety/depression associated with a cancer diagnosis, tobacco dependence, and MDD.

- A. Mystical experience
- B. Clarity
- C. Depression
- D. Anxiety

Question 2: Preliminary evidence of efficacy across multiple diagnoses and outcome domains suggests that?

- A. The mechanism of action generalises to various facets of mood, emotion, and cognition across a range of diagnoses
- B. There are several mechanisms of action spanning levels of analysis (e.g., molecular, circuit-level, psychological), with possible time-varying contributions
- C. None of the above

Question 3: The disruption and remodeling perspective emphasizes two distinct but possibly related temporal facets of psilocybin and psychedelics more broadly.

- A. TRUE
- B. FALSE

Question 4: Of relevance to the _____ phase is the behavioral catalyst model, which proposes that psychedelics catalyze the PST component to overcome blocks to a successful psychotherapeutic resolution.

- A. Remodeling
- B. Preparation
- C. Disruption
- D. Integration

Question 5: _____ have been engineered and shown to exert favourable behavioural effects in animal models, and such compounds are already being developed commercially for investigation in humans.

- A. Non-traditional SSRIs (selective serotonin reuptake inhibitors)
- B. Dopamine agonists
- C. Non-psychedelic psychoplastogen compounds

Question 6: The _____ therapeutic effects of psilocybin, manifesting in the span of hours, are likely largely mediated by processes occurring in the disruption phase.

- A. Delayed onset
- B. Long-term chronic
- C. Medium-term
- D. Rapid-onset acute

Question 7: Other theories of therapeutic mechanisms also emphasise the remodeling period, including which the following? Select all correct options.

- A. Elimination of trauma memories
- B. Post-acute enhancement of psychological and cognitive flexibility
- C. Feelings of connectedness, restoration of personal meaning
- D. Potential anti-inflammatory effects

Question 8: Potentiation of processes in the remodeling phase could include?

- A. Delivery of enhanced forms of psychotherapy
- B. Delivery of enhanced forms of cognitive/affective training to promote adaptive learning in concert with putative enhanced neuroplasticity
- C. The delivery of therapeutic neuromodulation to synergise with psilocybin-induced remodeling potential.

Question 9: Little is known regarding how concomitant _____ may impact the efficacy of psilocybin with PST.

- A. Physical activity
- B. Psychoanalysis
- C. Psychiatric medications
- D. Use of cannabis

Question 10: Alkaloid levels vary with passage of time and the conditions and methods used for processing and storage. Thus, patients should be counselled that use of natural mushroom products should not be considered as a substitute for the precise dosing and purity offered by synthetic pharmaceutical-grade psilocybin, and it is not currently possible to draw parallel conclusions between the two regarding safety and efficacy.

- A. TRUE
- B. FALSE

THE END



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C10(26)

Psilocybin: From Psychiatric Pariah to Perceived Panacea

PART 1						PART 2						PART 3					
	A	B	C	D	E		A	B	C	D	E		A	B	C	D	E
1						1						1					
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