Psychopharmacology (2022) 239:1907–1932
https://doi.org/10.1007/s00213-021-06049-6

REVIEW

Assessing the risk–benefit profile of classical psychedelics: a clinical review of second-wave psychedelic research

David Bender[1] · **David J. Hellerstein**[2,3]

Received: 11 August 2021 / Accepted: 20 December 2021 / Published online: 13 January 2022

Abstract

Rationale A broad reassessment of the potential benefits of psychedelic drugs has led to the initiation of multiple major clinical trials in an effort to advance their status to become FDA-approved medications, as well as local legislative efforts to legalize or decriminalize their use.

Objectives To use recently published data to assess potential risks and benefits of psychedelic drugs as therapeutics, as well as to synthesize what is currently known in order to generate fruitful future research directions.

Methods A review of studies conducted since 1991 identified 14 clinical trials of classical psychedelics, including 11 of psilocybin ($N=257$ participants), 1 of lysergic acid diethylamide ($N=12$ participants), and 2 of ayahuasca ($N=46$ participants). Other published studies (e.g., of healthy volunteers, survey studies, case reports, neuroimaging) were also considered for review.

Results Published studies since 1991 largely support the hypothesis that small numbers of treatments with psychedelic-assisted psychotherapy can offer significant and sustained alleviation to symptoms of multiple psychiatric conditions. No serious adverse events attributed to psychedelic therapy have been reported. Existing studies have several limitations, including small sample sizes, inherent difficulty in blinding, relatively limited follow-up, and highly screened treatment populations.

Conclusions Substantial data have been gathered in the past 30 years suggesting that psychedelics are a potent treatment for a variety of common psychiatric conditions, though the ideal means of employing these substances to minimize adverse events and maximize therapeutic effects remains controversial. Unique factors related to study design are vital for clinical researchers in the field to address.

Keywords Psychedelics · Psilocybin · LSD · Ayahuasca · Clinical review · Depression · Hallucinogens · Adverse events

Abbreviations

LSD	Lysergic acid diethylamide
MDMA	3,4-Methylenedioxymethamphetamine
PTSD	Post-traumatic stress disorder
HPPD	Hallucinogen persisting perception disorder
MDD	Major depressive disorder
MEQ	Mystical Experience Questionnaire
BPD	Borderline personality disorder
QIDS	Quick Inventory of Depression Symptoms
BDI	Beck Depression Inventory
HADS	Hospital Anxiety and Depression Scale
STAI	State-Trait Anxiety Inventory
GAD	Generalized anxiety disorder
GRID-HAM-D	GRID Hamilton Depression Scale
HAM-A	Hamilton Anxiety Scale
DMN	Default mode network

This article belongs to a Special Issue on Psychopharmacology on Psychopharmacology on Psychedelic Drugs

✉ David J. Hellerstein
David.hellerstein@nyspi.columbia.edu

[1] Department of Psychiatry, Washington University in St. Louis School of Medicine, St. Louis, MO, USA

[2] Columbia University Department of Psychiatry, New York, NY, USA

[3] New York State Psychiatric Institute, 1051 Riverside Drive, Unit #51, New York, NY 10032, USA

Introduction

Psychedelic plants have been used by humans for thousands of years (Schultes et al. 2001), generally in structured ceremonial settings (Myerhoff 1974; Fernandez 2019). Lysergic acid diethylamide (LSD), first synthesized in 1938, became a commonly used psychiatric treatment over the following decades. Over a thousand papers on LSD were published between 1950 and 1970 (Grinspoon and Bakalar 1979), evaluating its potential utility across numerous different patient populations, with clinical efficacy best established for the treatment of substance use disorders and end-of-life-related mood disorders (Krebs and Johansen 2012; Ross 2018). In 1970, the Controlled Substances Act categorized major psychedelic drugs as Schedule I compounds, leading to the cessation of most clinical research (Grinspoon and Bakalar 1979).

There has been a recent resurgence of interest in therapeutic applications of psychedelic drugs (Yaden et al. 2021). Since 1991, numerous research studies of classical psychedelic drugs—including psilocybin, LSD, and ayahuasca—in human participants have been published, reporting on 343 participants in clinical trials and over 1800 healthy volunteers (Fig. 1). Research centers into therapeutic uses of psychedelics have been founded at several major medical research institutions, and the Clinicaltrials.gov federal registry lists dozens of ongoing trials for classical psychedelics. Two phase II trials evaluating the safety and efficacy of psilocybin for the treatment of major depressive disorder (MDD) have been initiated, and positive results from the Compass Pathways Phase IIb trial have been announced but not yet published. Though most early research was funded privately, the UK government has funded some recent psychedelic studies (https://reporter.nih.gov/search/_NuFp5PaT0alcI1JOIRGVA/project-details/1012733), and NIDA has recently funded a study of psilocybin for tobacco dependence.

Shifting public sentiment toward psychedelics is evident in increasing media attention, major investments in companies developing psychedelic therapy, and local legislative initiatives altering laws curbing psychedelic usage, including approval for therapeutic use of psilocybin mushrooms in Oregon and decriminalization of psilocybin mushrooms in several cities. However, psychedelics retain federal Schedule I designation, and most research continues to be funded by philanthropists and entrepreneurs rather than federal government agencies.

In addition to causing alterations in perception connoted by the term "hallucinogen," these compounds frequently induce intense emotional experiences that are contingent upon traits of the user and the environment in which the drug is taken, characterized as the "set and setting" of drug ingestion (Carhart-Harris et al. 2018a). Common effects include euphoria, the induction of intense and memorable emotional experiences, anxiety, and emotional lability, as

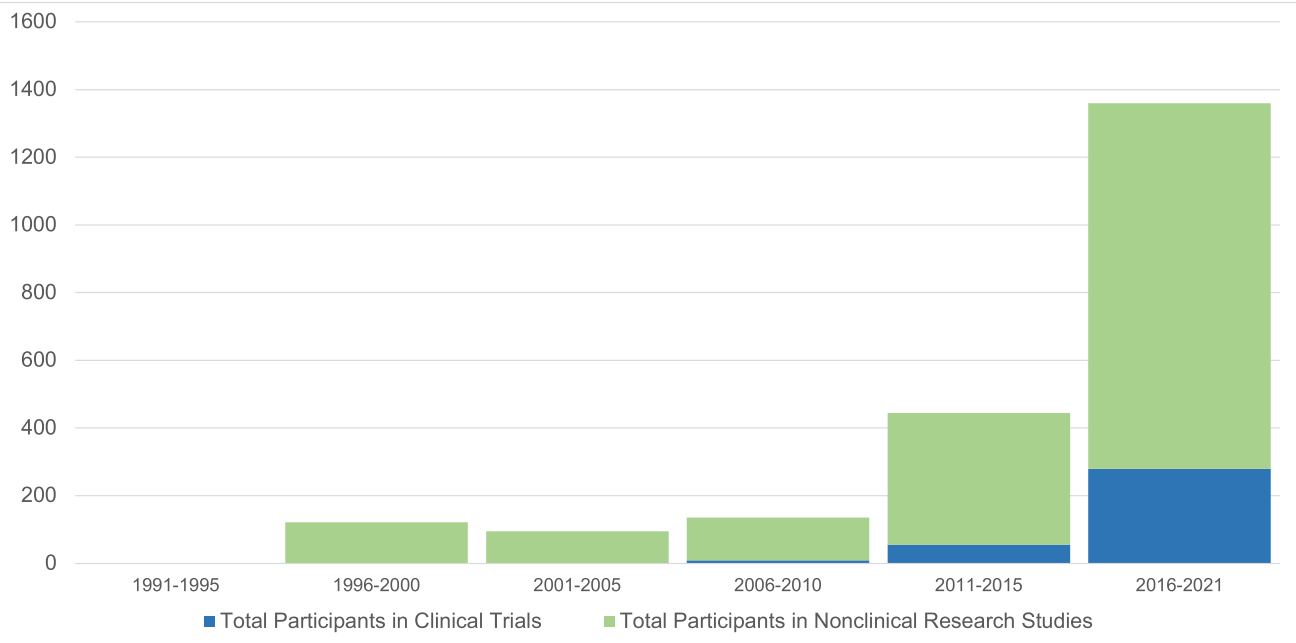

Fig. 1 Participation in controlled psychedelic research studies involving psilocybin, LSD, and ayahuasca since 1991. Participants in naturalistic studies during which the drug was not provided by the research group were not included in totals

well as transient psychotic symptoms such as delusions, impaired reality testing, and hallucinations (Watts et al. 2017; Strassman 1984). Studies have correlated clinical outcomes to an individual's appraisal of their experience, suggesting that this is a relevant factor in therapeutic outcomes (Griffiths et al. 2016; Ross et al. 2016; Davis et al. 2020; Garcia-Romeu et al. 2014; Roseman et al. 2017). Accompanying psychotherapy is viewed as critical to guiding these experiences; hence, psychedelic treatments can be viewed as combined medication and psychotherapy treatments (Carhart-Harris et al. 2018a).

This critical review offers an overview of recent studies of classical psychedelics psilocybin, LSD, and ayahuasca to assess the risk–benefit profile of psychedelic therapies, with emphases on strengths and limitations of existing research. Discussions of methodology, dosing, and therapeutic mechanisms offer further insight into these topics. Future research directions are discussed in the context of limitations of existing findings and the unique nature of psychedelic treatments.

Methods

Goals of review

The aim of this review is to summarize and critically analyze the methods and results of recent clinical studies of the three classical psychedelics used in treatment of psychiatric patients since 1991: psilocybin, LSD, and ayahuasca. We sought to provide a summative assessment of risks and benefits of psychedelic psychotherapy, and to offer a critical discussion to assist in the development of future clinical trials. We reviewed available efficacy data and assessed key aspects of study methodology, adverse effects, and dosing strategies. PRISMA guidelines served as guiding principles for this review. Additional data sources were used to provide a broad overview and to characterize potential risks and benefits of psychedelic psychotherapy. Due to significant heterogeneity across studies reviewed, meta-analysis was not performed. This review was not pre-registered.

MDMA was excluded from this review because it has a distinct mechanism of action and subjective effects relative to classical psychedelics (Holze et al. 2020). Mescaline, dimethyltryptamine (DMT), and 5-methoxy-N,N-dimethyltryptamine (5MeO-DMT), though generally considered classical psychedelic compounds, were excluded because there have been no published clinical trial data within the timeframe of this review.

Selection of data

A literature search for classical psychedelics (psilocybin, LSD, and ayahuasca) was performed using PubMed, with older reviews used as supplements (Andersen et al. 2021), within dates of January 1, 1991–June 1, 2021. Search terms included "psilocybin," "LSD AND lysergic acid diethylamide," and "ayahuasca." All published studies including psilocybin/LSD/ayahuasca being given to human participants were tallied, enabling a quantitative summary of increasing scientific interest in these compounds (Fig. 1).

Abstracts identified in this search were reviewed by D.B. to assess whether psychedelic treatments were studied in clinical populations across all diagnostic categories. This list was narrowed to studies offering both consistent treatment methodology across all enrolled patients and assessing clinical endpoints (Fig. 2).

Studies identified by D.B. and reviewed by both authors are presented in the clinical trial section of Table 1. There was a consensus that 14 studies listed met these criteria. Several studies performed in healthy volunteers, reviewed by D.B. and D.H., are included in Table 1 on the basis of their perceived relevance to psychedelic drug treatment on methodological issues, adverse event profiles, and dosing strategies. They do not represent a comprehensive overview of studies of psychedelics in healthy volunteers. Additional publications (e.g., survey studies, case reports of recreational use, imaging studies, pre-1991 publications) were included to add context to recent clinical findings, but this literature was not reviewed using specific search criteria.

Fourteen clinical trials identified enrolled 315 patients who received psychedelic drug treatments. Six were open label studies enrolling 89 participants, and 8 were double-blind studies enrolling 226 participants (plus 28 additional patients with depression from an ayahuasca study assessing physiological but not clinical outcomes), for a total of 343 total patients with psychiatric diagnoses receiving treatment, as shown in Fig. 1. Data from the Compass Pathways Phase IIb trial of psilocybin, which were released in November 2021 but remain unpublished at the time of this review, are not included.

Results subsections

Study results are divided into five specific subsections: (A) *Physiological and adverse events*; (B) *Study methodology*; (C) *Treatment efficacy*; (D) *Dosing*; and (E) *Mechanisms*. *Physiological and adverse events* draws on the results of recent clinical literature and healthy volunteer studies in addition to other literature (e.g., survey studies, earlier reviews, case reports) to provide a summary of the adverse response profile to psychedelics. *Study methodology* describes the basic approach to the administration of psychedelic drugs in the context of therapeutic studies and draws on data from clinical and nonclinical studies to discuss the unique methodological issues relevant to designing clinical trials involving psychedelic compounds. *Treatment efficacy*

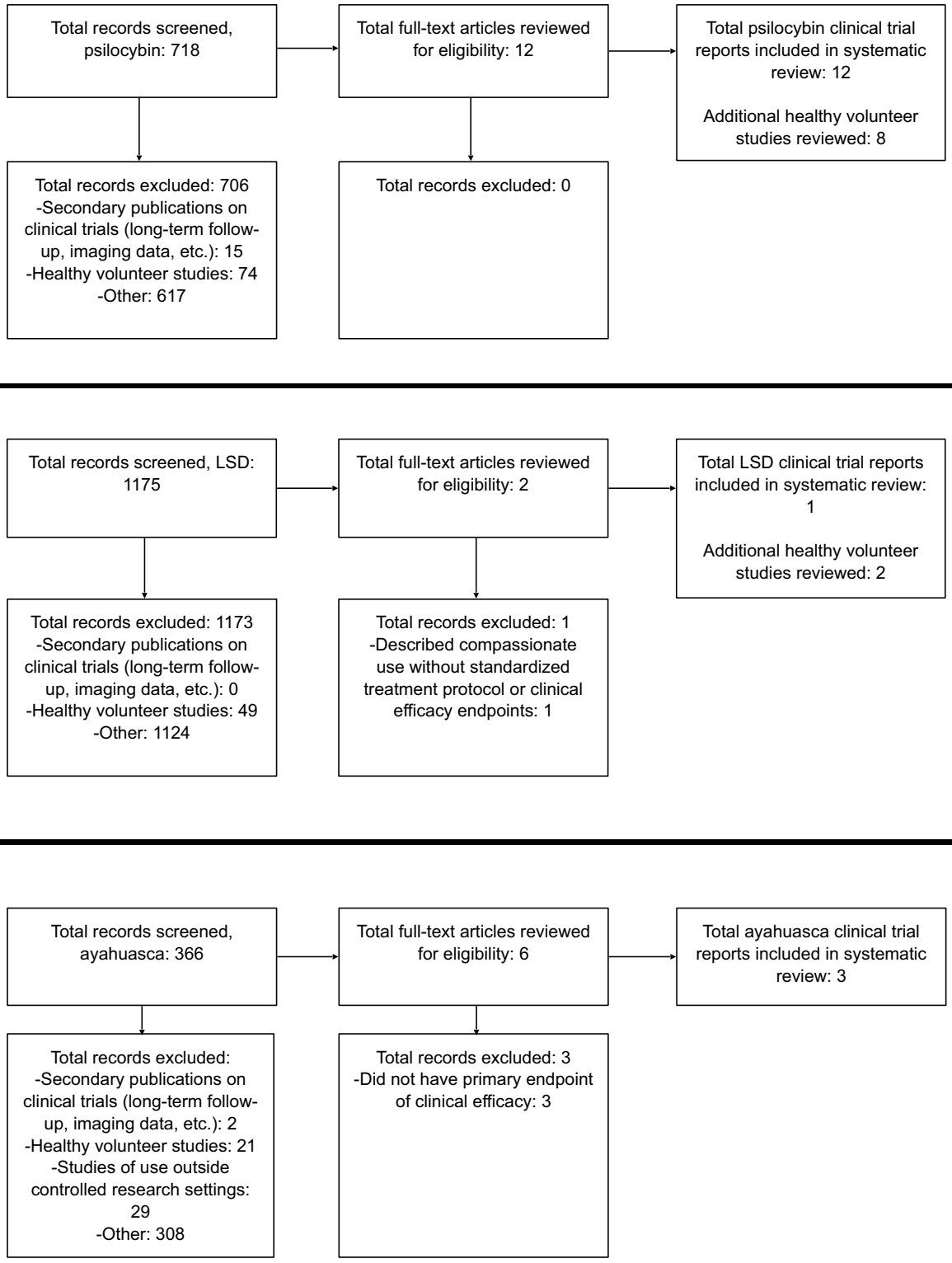

Fig. 2 Flowsheet for the identification of studies of psilocybin, LSD, and ayahuasca

summarizes the results of major recent clinical trials of classical psychedelics. *Dosing* synthesizes results of human studies of psilocybin in clinical and nonclinical populations to offer suggestions for dosing protocols in future studies. *Mechanisms* draws on both clinical trial data and other literature (e.g., imaging studies, theoretical publications, healthy

Table 1 Overview of psychedelic clinical trials and select healthy volunteer studies from 1991 to 2021

Study	Treatment population	Drug	Subjects (*N*)[a]	Design	Active dose(s)	# Active treatment sessions	Screening proportion[b]	Hours of supporting therapy	Type of supporting therapy[c]	% College educated	Race	Prior hallucinogen use	Major treatment outcomes	Duration of follow-up	% Significant dysphoric reactions
Clinical trials															
Moreno et al. 2006	OCD with ≥ 1 treatment failure	Psilocybin	9	Open-label, dose escalation	0.1, 0.2, 0.3 mg/kg	3	NR	NR	NR	NR	NR	100%	66.7% participants with ≥ 50% decrease in Yale-Brown Obsessive–Compulsive score at 24 h for at least 1 dose, 11.1% long-term remission	6 months	0%
Grob et al. 2011	Cancer patients with anxiety disorders	Psilocybin	12	Randomized crossover study with active placebo control (niacin)	0.2 mg/kg	1	NR	NR	Basic	NR	NR	67%	STAI trait anxiety significantly reduced at 1 and 3 months after treatment, trends toward improvement in BDI scores in treatment group	Minimum 3 months	0%
Johnson et al. 2014	Tobacco addiction	Psilocybin	15	Open-label	0.29, 0.43 mg/kg	2–3	8%	14.5	Addiction-oriented CBT	73%	93% white	67%	67% abstinent at 12 months	12 + months	40%
Bogenschutz et al. 2015	Alcohol use disorder	Psilocybin	10	Open-label	0.3, 0.4 mg/kg	1–2	NR	12	Motivational enhancement therapy	30%	40% Hispanic, 30% white	NR	Significant reduction in heavy drinking days after first treatment, strong correlation ($r = 0.76$–0.89) between acute drug effects and outcomes	36 weeks	NR

Table 1 (continued)

Study	Treatment population	Drug	Subjects (*N*)[a]	Design	Active dose(s)	# Active treatment sessions	Screening proportion[b]	Hours of supporting therapy	Type of supporting therapy[c]	% College educated	Race	Prior hallucinogen use	Major treatment outcomes	Duration of follow-up	% Significant dysphoric reactions
Griffiths et al. 2016	Cancer patients with depression and/or anxiety symptoms	Psilocybin	51	Randomized crossover study with active placebo control (low-dose psilocybin)	0.31 mg/kg, 0.43 mg/kg	1	10%	15	Basic	98%	94% white	45%	HAM-D depression scores: 92% response and 60% remission at 5 weeks in treatment group vs. 32% and 16% for active-placebo, improvements largely persistent at 6 months, outcomes correlated with subjective experience ratings	6 months	32%
Ross et al. 2016	Cancer patients with depression and/or anxiety	Psilocybin	29	Randomized crossover study with active placebo control (niacin)	0.3 mg/kg	1	39%	18	Existentially-oriented psychotherapies	79%	90% white	55%	BDI depression score: ~ 80% remission at 7 weeks in treatment group vs. ~ 10% in active placebo group, antidepressant/anxiolytic response rates 60–80% at 6 months, outcomes correlated with subjective experience ratings	6 months	17% anxiety, 7% psychotic symptoms

Table 1 (continued)

Study	Treatment population	Drug	Subjects (*N*)[a]	Design	Active dose(s)	# Active treatment sessions	Screening proportion[b]	Hours of supporting therapy	Type of supporting therapy[c]	% College educated	Race	Prior hallucinogen use	Major treatment outcomes	Duration of follow-up	% Significant dysphoric reactions
Carhart-Harris et al. 2016, 2018	Treatment-resistant depression	Psilocybin	20	Open-label	10 mg, 25 mg	2	27%	NR	Basic	90%	75% white	35%	Significant reductions in depressive symptoms at 5 weeks (Cohen's $d = 2.3$), with sustained results at 6 months (Cohen's $d = 1.4$), outcomes correlated with subjective experience ratings	6 months	Transient anxiety 75%, transient paranoia 15%
Davis et al. 2020	Major depression	Psilocybin	24	RCT, patients randomized to either immediate or delayed treatment	0.29, 0.43 mg/kg	2	3%	10	Basic	83%	92% white	Mean lifetime use = 0.8	Significant reductions in depressive symptoms at 4 weeks post-treatment in immediate treatment group vs. delayed (Cohen's $d = 3.3$), 54% in remission 4 weeks post treatment, in immediate treatment group, improvements correlated with subjective experience ratings	4 weeks	Up to 90%

Table 1 (continued)

Study	Treatment population	Drug	Subjects (*N*)[a]	Design	Active dose(s)	# Active treatment sessions	Screening proportion[b]	Hours of supporting therapy	Type of supporting therapy[c]	% College educated	Race	Prior hallucinogen use	Major treatment outcomes	Duration of follow-up	% Significant dysphoric reactions
Anderson et al. 2020a, b	HIV/AIDS-related demoralization	Psilocybin	18	Open-label	0.3, 0.36 mg/kg	1	20%	15–18	Brief supportive expressive group therapy	72%	78% white	Median use = 5	Clinically meaningful reduction in demoralization at 3 months (standardized effect size estimate drm = 0.97)	3 months	44% severe anxiety, 22% paranoia, 6% thought disorder
Schindler et al. 2021	Migraine headache	Psilocybin	10	Randomized crossover study with placebo control	0.14 mg/kg	1	NR	NR	Basic	NR	100% white	20%	Significant decrease in migraine frequency in treatment group for 2 weeks after treatment, no correlation between subjective effects and change in migraine frequency	3 months	0%
Carhart-Harris et al. 2021	Major depression	Psilocybin	59	RCT, treatment arms escitalopram + psilocybin 1 mg vs. psilocybin 25 mg	25 mg	2	6%	12[d]	Basic	73%	88% white	27%	No significant difference in change in QIDS-SR16 scores when comparing treatment arms, 70/57% response/remission rates in psilocybin arm vs. 57/28% in escitalopram arm, most secondary analyses favored psilocybin arm	6 weeks	NR

Table 1 (continued)

Study	Treatment population	Drug	Subjects (*N*)[a]	Design	Active dose(s)	# Active treatment sessions	Screening proportion[b]	Hours of supporting therapy	Type of supporting therapy[c]	% College educated	Race	Prior hallucinogen use	Major treatment outcomes	Duration of follow-up	% Significant dysphoric reactions
Gasser et al. 2014	Anxiety associated with life-threatening diseases	LSD	12	Randomized crossover study with active placebo control (low-dose LSD)	200 mcg	2	17%	NR	Basic	NR	NR	8%	Trends toward reduction in STAI trait anxiety at 2-month follow-up, sustained at 12 months	12 months	22.7% anxiety, 36.4% emotional distress
De L Osório et al. 2015; Sanches et al. 2016[e]	Major depression	Ayahuasca	17	Open-label	120–200 mL ayahuasca with 0.8 mg/mL DMT and 0.21 mg/mL harmine	1	NR	Admitted to inpatient floor 2 weeks prior to treatment	Limited[f]	NR	NR	NR	Mean HAM-D scores significantly decreased 3 weeks post-treatment	21	0%
Palhano-Fontes et al. 2019	Treatment-resistant depression	Ayahuasca	29	RCT with active placebo control (placebo with unpleasant taste, induced nausea)	0.36 mg/kg N,N-DMT	1	16%	Admitted to inpatient floor 2 weeks prior to treatment	Limited[f]	17%	59% Caucasian	NR	Mean HAM-D score significantly decreased relative to placebo group at 1 week (Cohen's $d = 0.98$), 43% treatment group in remission at 1 week vs. 13% placebo	7	NR
Selected healthy volunteer studies															
Hasler et al. 2004	Healthy volunteers	Psilocybin	8	Double-blind study of placebo, multiple psilocybin doses	0.045, 0.115, 0.215, 0.315 mg/kg	4	NR	NR	NR	NR	NR	NR	Psilocybin dose-dependently produced increases in physiological measures, subjective experience scores	NR	12.5% with transient anxiety
Griffiths et al. 2006	Healthy volunteers	Psilocybin	36	Randomized crossover study with active placebo control (methylphenidate)	0.43 mg/kg	1–2	27%	16–20	Basic	97%	NR	0%	61% of psilocybin arm met criteria for a complete mystical experience vs. 11% of methylphenidate arm	14 months	31%

Table 1 (continued)

Study	Treatment population	Drug	Subjects (*N*)[a]	Design	Active dose(s)	# Active treatment sessions	Screening proportion[b]	Hours of supporting therapy	Type of supporting therapy[c]	% College educated	Race	Prior hallucinogen use	Major treatment outcomes	Duration of follow-up	% Significant dysphoric reactions
Griffiths et al. 2011	Healthy volunteers	Psilocybin	18	Open-label, dose escalation or de-escalation	0.07, 0.14, 0.29, 0.43 mg/kg	4	6%	18	Basic	94%	NR	6%	72% of participants met criteria for a full mystical-type experience for at least one dosing, which only occurred at 0.29 mg/kg and 0.43 mg/kg doses	14 months	39% (across all dosings)
Nicholas et al. 2018	Healthy volunteers	Psilocybin	12	Open-label	0.3, 0.45, 0.6 mg/kg	3	10%	14	Basic	NR	75% white	100%	36% of all doses facilitated a complete mystical-type experience, similar rates across dose levels	1 month	0%
Griffiths et al. 2018	Healthy volunteers	Psilocybin	75	RCT with active-placebo control (low-dose psilocybin)	0.29, 0.43 mg/kg	2	7%	7–35	Spiritual practice support	89%	85% white	27%	High-dose groups with increased ratings on metrics of personal spirituality	6 months	NR
Carbonaro et al. 2018	Healthy volunteers	Psilocybin	20	Double-blind study of placebo, multiple psilocybin doses, high-dose dextromethorphan (DXM)	0.14, 0.29, 0.43 mg/kg psilocybin, 400 mg/70 kg DXM	3	54%	8	Basic	50%	95% white	100%	20% and 40% rates of complete mystical-type experiences after 0.29 mg/kg and 0.43 mg/kg psilocybin, 0% after DXM, placebo, 0.14 mg/kg psilocybin	NR	NR
Madsen et al. 2019	Healthy volunteers	Psilocybin	10	Open-label	0.2, 0.3 mg/kg	1	NR	NR	Limited[g]	NR	NR	0%	Increase in metrics of mindfulness at 3 months	3 months	NR

Table 1 (continued)

Study	Treatment population	Drug	Subjects (*N*)[a]	Design	Active dose(s)	# Active treatment sessions	Screening proportion[b]	Hours of supporting therapy	Type of supporting therapy[c]	% College educated	Race	Prior hallucinogen use	Major treatment outcomes	Duration of follow-up	% Significant dysphoric reactions
Barrett et al. 2020	Healthy volunteers	Psilocybin	12	Open-label	0.36 mg/kg	1	NR	8	Basic	83%	100% white	100%	Psilocybin reduced scores of negative affect and increased scores of positive affect at 1 week	NR	NR
Liechti et al. 2017	Healthy volunteers	LSD	40	Pooled data from two randomized placebo-controlled crossover studies	100 mcg, 200 mcg	1	NR	NR	Limited[g]	NR	NR	28%	Increased subjective experience scores at 200 mcg compared to 100 mcg and placebo, 10% met criteria for complete mystical experience	NR	NR
Holze et al. 2021	Healthy volunteers	LSD	16	Double-blind study of various LSD doses, placebo	25, 50, 100, 200 mcg	4	NR	NR	Limited[g]	NR	NR	38%	LSD dose-dependently increased subjective effects, ceiling effect for good drug effects at 100mcg	NR	Significant anxiety reported at 200 mcg dose

[a]Subjects were only included in Table if their data was included in final study analyses

[b]Proportion: study participants enrolled/number screened, usually by telephone but occasionally including online surveys

[c] "Basic therapy" includes meeting with therapists prior to and after treatment to build rapport/discuss treatment sessions and drug administration in a comfortable setting with music and psychological support from therapists

[d]Each integration session was assumed to last 1 h to determine this total

[e]Data from two publications for one trial

[f]Therapists were not consistently present in treatment room during dosing, minimal additional psychotherapy

[g]Minimal accompanying psychotherapy outside of dosing days

volunteer studies, animal studies) to briefly introduce key theories seeking to explain the therapeutic action of psychedelic compounds.

Data assessment and summary

Data extracted from clinical and nonclinical studies reviewed included the following: results of major clinical or nonclinical endpoints and measures of statistical significance; traits of study populations; approach and amount of accompanying psychotherapy; dosing approaches; efficacy of blinding procedures; correlations between subjective effects and clinical improvement; and rates of adverse psychological events. These are described in the "Results" section and summarized in Tables 1 and 2.

Results

Physiological and adverse effects

The adverse effect profile of classical psychedelics is distinct from most existing psychopharmacological treatments. For decades, the risks of psychedelics may have been exaggerated due to social stigmatization (Johansen and Krebs 2015), heightened by claims from the 1960s that LSD caused chromosomal damage and birth defects, which were later rebutted (Dishotsky et al. 1971). A nuanced understanding of risks is relevant for clinicians to assess the relative utility of psychedelic treatments, and for counseling patients considering self-medication outside controlled environments. This section focuses on psilocybin (because most recent clinical data has been gathered regarding this substance), but data from other classical psychedelics are also considered. Table 2 offers a summary of adverse event profiles of classical psychedelics within controlled research settings obtained from recent studies.

Acute physiological effects

When taken orally in doses used during clinical studies, psilocybin produces an altered state of consciousness that typically begins within 20–40 min after ingestion, reaches maximum effect within 60–90 min, and usually subsides within 3–6 h (Passie et al. 2002). Psilocybin is a prodrug of psilocin, and serum concentrations of psilocin have been found to correlate with both subjective drug effects and 5-HT_{2A} receptor occupancy (Madsen et al. 2019), which has been shown to be the predominant receptor mediating psychedelic subjective effects (Vollenweider et al. 1998;

Table 2 Qualitative summary of adverse effects of psychedelic drugs in recent clinical studies

Adverse event	Category	Onset after dosing	Severity	Frequency[a]
Nausea	Physical	Acute	Mild	Common
Vomiting	Physical	Acute	Mild	Rare
Fatigue, headache	Physical	Acute/subacute	Mild	Common
Hypertension	Physical	Acute	Mild-moderate	Common
Tachycardia	Physical	Acute	Mild	Occasional
Other cardiac events	Physical	Acute	Mild-severe	Not reported
Ataxia	Physical	Acute	Mild	Occasional
Hospitalization	Physical	Acute	Severe	Not reported
Dysphoria (anxiety, sadness, etc.)	Psychiatric	Acute	Mild	Common
Transient psychotic symptoms	Psychiatric	Acute	Mild-moderate	Occasional
Sustained psychosis	Psychiatric	Subacute-chronic	Severe	Not reported
HPPD	Psychiatric	Subacute-chronic	Mild-moderate	Not reported
Persistent psychological instability	Psychiatric	Subacute-chronic	Mild-moderate	Rare
Self-harm	Psychiatric	Subacute	Mild-severe	Rare[b]
Suicide attempts, suicide	Psychiatric	Subacute	Severe	Not reported[c]
Sustained cognitive impairment	Psychiatric	Subacute-chronic	Mild-severe	Not reported
Addiction, physical dependency	Psychiatric	Subacute-chronic	Moderate	Not reported

[a]Rare is defined as < 2%; occasional as 2 to 20%; common as > 20%. These should be understood as approximations on the basis of available data, and may not be generalizable to all treatment populations or settings of use

[b]See Anderson et al. (2020a, b) for details of a reported case of self-harm, which appears to be unrelated to psilocybin therapy

[c]See the supplemental materials of Griffiths et al. (2016) for discussion of a completed suicide which occurred within two weeks of a psilocybin dosing session. This event occurred in the placebo-dose psilocybin arm of the study (1 mg) and was not attributed to psilocybin therapy

Liechti 2017). Psilocybin causes clinically insignificant increases QTc interval at doses used in research studies to date (Dahmane et al. 2021) and clinically insignificant increases in serum liver enzymes at high doses (Hasler et al. 2004). Though psychedelic-induced, clinically significant hypertension is uncommon, some participants have developed systolic blood pressures over 160 mmHg and diastolic over 100 mmHg. This is more common in older patients with underlying medical conditions (Griffiths et al. 2016; Anderson et al. 2020a). Early reviews reported pupillary dilation, nausea, vomiting, tremor, hyperreflexia, dizziness, and ataxia (Strassman 1984; Passie et al. 2002). In recent clinical trials, nausea has been commonly reported (Griffiths et al. 2016; Ross et al. 2016; Anderson et al. 2020a; Carhart-Harris et al. 2021). Vomiting is uncommon with psilocybin, though has been reported in recent studies (Griffiths et al. 2016; Bogenschutz et al. 2015). It is much more common with ayahuasca (Palhano-Fontes et al. 2019). Other acute side effects include occasional ataxia (Anderson et al. 2020a; Gasser et al. 2014), feeling cold (Gasser et al. 2014), motor agitation/restlessness (Anderson et al. 2020a), hyperhidrosis (Gasser et al. 2014), diarrhea (Bogenschutz et al. 2015), and urinary incontinence (Anderson et al. 2020a). Subacutely, the most common physical adverse effects are headache and fatigue, which generally resolve within 24 h (Johnson et al. 2012).

No participants in recent studies have required medical hospitalization. The reported LD_{50} of psilocybin in mice is 280 mg/kg, while a high therapeutic dose in humans is 0.43 mg/kg (Cerletti 1958). Individuals with significant underlying cardiovascular, neurologic, hepatic, or renal conditions have largely been excluded from recent studies, and it is unclear whether medical complications will be more common in these populations. Life-threatening medical complications have occurred in individuals taking unregulated classical psychedelics (including psilocybin-containing mushrooms) in uncontrolled settings, though even in these settings, medical fatalities are extremely rare and likely multifactorial (Bickel et al. 2005; Raval et al. 2008; Berrens et al. 2010; Aakeroy et al. 2020; Borowiak et al. 1998; Nichols and Grob 2018; Lim et al. 2012; Leonard et al. 2018). Though classical psychedelics have overlapping neurophysiological mechanisms, their adverse effect profile may not be uniform. A recent analysis of calls to US poison centers reported cardiac arrests, respiratory arrests, seizures, and several fatalities apparently related to ayahuasca use, though adverse event reports of recreational use are hindered by numerous potential confounders (Heise and Brooks 2017). The presence of MAOIs in ayahuasca may increase risk for severe drug–drug interactions with prescription, herbal, or over the counter drugs (Malcolm and Thomas 2021). Psychedelics' safety profile may also be impacted by drug-drug interactions, especially with psychiatric medications, as highlighted by a recent online forum analysis study that found an association between psychedelic coadministration with lithium and seizures (Nayak 2021).

Acute psychological effects

Classical psychedelics cause dose-dependent alterations in consciousness affecting perception, cognition, and emotional state. The intensity of both euphoric and dysphoric emotional effects, as well as of sensory alterations, is correlated to increasing dose (Griffiths et al. 2011; Studerus et al. 2011). Positive or euphoric effects are variously described, and may include loss of sense of self, a sense of timelessness, and feelings of emotional catharsis, forgiveness, or self-compassion (Watts et al. 2017; Studerus et al. 2011; Gasser et al. 2015; Belser et al. 2017). One common scale for quantifying subjective effects is the Mystical Experience Questionnaire (MEQ), which scores four dimensions of a "mystical experience": sacredness, positive mood, transcendence of time/space, and ineffability (Maclean et al. 2012). Other scales used to quantify subjective effects of hallucinogens include the Hallucinogen Rating Scale (HRS), the Five Dimensions-Altered State of Consciousness scale (5D-ASC), and the Challenging Experiences Questionnaire (CEQ) (Strassman et al. 1994; Studerus et al. 2010; Barrett et al. 2016).

Dysphoric reactions are common in recent studies among both healthy volunteers and those with psychiatric conditions, with 31–39% of healthy participants reporting strong or extreme fear (Griffiths et al. 2006, 2011) and 40% of participants with MDD endorsing feelings of panic (Davis et al. 2020). Responses can be separated into negatively valenced emotions (grief, despair, or guilt), as well as effects resembling psychosis (paranoid delusions, thought disorder, and frightening hallucinations). Delusions in recent studies include beliefs that therapists were behaving malevolently, and that a loved one died during the treatment session (Griffiths et al. 2011).

The potential for dysphoric reactions likely varies on traits of the individual treated and the social context of drug administration. Early research suggested that subjects characterized as anxious, manipulative, hostile, or self-punitive were more likely to have dysphoric reactions (Langs and Barr 1968). Other studies assessed the effect of social context on response, which included findings that the intensity of negative effects was lowest when study staff acted in a friendly way, moderate when study staff behaved normally, and highest when study staff behaved indifferently (Hyde 1960). Reactions were also worse when taking LSD alone compared to when in groups. Recent studies have found that high emotional excitability, young age, and treatment setting involving brain imaging most strongly predicted dysphoric reactions (Studerus et al. 2012). A recent review suggested

high trait absorption and openness are related to a higher likelihood of euphoric experiences and lower levels are related to dysphoric experiences, while preceding psychological states of apprehension, confusion, or preoccupation are related to dysphoria (Aday et al. 2021).

Though acute dysphoric reactions might understandably be viewed as undesirable, their relationship to clinical outcomes is unclear. A recent study of psilocybin for MDD found a correlation between treatment efficacy and positively valenced subjective effects, but no correlation between the degree of dysphoria and treatment efficacy (Davis et al. 2020). Whether acute dysphoric reactions should be considered genuine adverse events is controversial, and the degree of reporting varies across published studies (Davis et al. 2020; Carhart-Harris et al. 2021).

Psychological risks of psychedelic drugs have been emphasized historically, in part due widespread use in uncontrolled settings. Recreational psychedelic use has been associated with acute adverse outcomes including emergency room visits for psychiatric management, putting self or others at risk of physical harm, suicide attempts, and accidental death (Nichols 2016; Carbonaro et al. 2016).

Sustained adverse effects

Recent studies suggest that psychedelic drugs, when used in controlled settings with well-screened participants who are offered appropriate preparation, supervision, and follow-up, are unlikely to cause prolonged psychiatric or neurologic complications.

Though psychedelics can acutely induce an altered state of consciousness resembling a psychotic state, their potential to induce sustained psychosis is unclear. Though there is no convincing evidence that psychedelics are a primary causal factor of persistent psychotic disorders, it has been suggested that they may be a precipitative factor inducing symptom onset in susceptible individuals (Strassman 1984). No reports of persistent psychotic symptoms have been noted in recent studies, though individuals with family histories of psychotic disorders have generally been excluded. In a recent online survey study of 1993 participants who described their most difficult experience taking psilocybin mushrooms recreationally, 0.15% described the onset of persistent psychotic symptoms after the experience, all of whom were aged 18–21, with one participant endorsing he was ultimately diagnosed with schizophrenia (Carbonaro et al. 2016). A recent case report describing a first manic episode in an individual with a family history of bipolar disorder that was apparently induced by psilocybin-containing mushrooms used recreationally further highlights this concern (Hendin and Penn 2021).

Hallucinogen persisting perception disorder (HPPD) is a DSM-5 diagnosis defined by recurrence of perceptual disturbances resulting from use of hallucinogenic drugs, which cause significant impairment. Recent reviews have concluded that while HPPD may cause significant morbidity for some individuals, the actual prevalence is difficult to ascertain, and clinically significant cases appear rare (Halpern and Pope 2003; Halpern et al. 2018). No cases have been reported following recent studies.

Given the prevalence of psychedelic-induced dysphoria, the concern arises that such experiences might induce persistent psychological instability. Within recent controlled studies, this has been rarely reported, and has generally resolved quickly. In a review of 110 healthy individuals taking psilocybin in experimental settings, 7 subjects reported negative changes in psychological well-being such as increased mood swings or concentration problems after treatment, though 6/7 considered them of low-intensity and temporary (Studerus et al. 2011). Of 250 individuals treated with psychedelics at Johns Hopkins including healthy volunteers and clinical trial participants, only 0.9% reported transient negative psychological effects after treatment, and none reported major or lasting psychological problems (Carbonaro et al. 2016). Several cases have been reported of individuals encountering repressed unpleasant or traumatic memories during or shortly after treatment, and the field is just beginning to develop guidance on how to address such events (Anderson et al. 2020a; Studerus et al. 2011; Johnson et al. 2017; Timmermann et al. 2020).

The risk for sustained adverse effects may differ outside controlled research settings. In a large survey study of individuals describing their most difficult experience using psilocybin mushrooms in recreational settings, 24% reported subsequently experiencing at least one psychiatric symptom following ingestion that lasted 1 week or longer, and 7.6% endorsed seeking professional help (Carbonaro et al. 2016). On a population level, psychedelic drug use is not associated with increased rates of mental health problems (Johansen and Krebs 2015; Hendricks et al. 2015). However, safety data on psychedelics in patients with significant mental illness are limited.

Recent clinical studies have not reported serious suicide attempts or suicides attributed to psychedelic therapy. However, individuals with histories of medically serious suicide attempts have been explicitly excluded from some studies of patients with relatively severe depression (Carhart-Harris et al. 2016a, 2021). One suicide was reported in a study of psilocybin-assisted therapy for treatment of cancer-associated anxiety and depression. Because this suicide occurred in a patient who first received placebo-dose (1 mg) in a crossover study, it was not attributed to the treatment (Griffiths et al. 2016). Though existing evidence does not suggest that the use of psychedelics in clinical settings increases suicidality, and some data suggest the opposite (Carhart-Harris et al. 2018b, 2021; Zeifman et al. 2021), the potential for

temporary psychedelic-induced emotional instability gives reason for caution in at-risk individuals.

Occasional, repeated use of classical psychedelics does not appear to cause sustained cognitive impairment (Halpern et al. 2005; Bouso et al. 2012; Grob et al. 1996). A review of early studies found some reports of mild impairment following LSD use in select cognitive tests, but these results were often not replicated, and most studies did not control for confounding factors (Halpern and Pope 1999). There have been no reports of sustained cognitive impairment in recent studies of LSD or psilocybin.

Though psychological tolerance to psychedelics is known to build within days of exposure, physical dependence does not develop (Abramson et al. 1957), which may be related to rapid downregulation of $5HT_{2A}$ receptors after ingestion demonstrated in animal models (Buckholtz et al. 1990; Gresch et al. 2005). Classical psychedelics are not considered addictive (Nichols 2016; Johnson et al. 2018), and animal studies have demonstrated that psychedelic drugs do not have significant reinforcing effects (Griffiths et al. 1980; Fantegrossi et al. 2004). Drug seeking behaviors have not been observed following most recent studies, though occasional reports exist (Carhart-Harris et al. 2018b). Whereas recreational use of most Schedule 1 drugs correlates with increased use of other drugs, following psychedelic use, data exists suggesting a spontaneous reduction in the consumption of addictive drugs (Garcia-Romeu et al. 2019a, b). Psychedelics have been used in clinical settings to successfully treat addiction to other substances (Krebs and Johansen 2012; Bogenschutz et al. 2015).

Study methodology

Recent studies using psychedelics have employed a treatment model combining biological and psychotherapeutic approaches to treatment. This section describes fundamentals of the psychedelic therapy model pursued in most recent studies, and its associated challenges.

Set and setting

The concept of "set and setting" in relation to psychedelic drug use was popularized in the 1960s by psychologist and psychedelic advocate Timothy Leary. "Set," or mindset of the drug user, and "setting" of drug ingestion—including the physical, social, and cultural environment—are hypothesized to play key roles in subjective experiences of psychedelic use (Leary 2000). Consistent with this principle, wide variability in subjective experience exists even in controlled settings, with individuals in recent studies describing treatment as the most meaningful as well as the most painful experience of their lives (Griffiths et al. 2006; Bogenschutz et al. 2018). The characteristics of subjective experience as quantified by the MEQ have been found to correlate with treatment outcomes (Griffiths et al. 2016; Ross et al. 2016; Davis et al. 2020; Garcia-Romeu et al. 2014; Roseman et al. 2017; Bogenschutz et al. 2015).

Recent studies have often sought to optimize set and setting by establishing rapport with study staff prior to treatment, providing adequate psychological preparation for dosing including describing possible drug effects, offering continuous psychological support and playing music during treatment, and providing follow-up therapy to discuss and integrate experiences (Johnson et al. 2008). While describing possible effects to participants may create confounding expectancy effects, it has been considered unethical to do otherwise. Treatments generally take place in comfortable, living room-like settings rather than in clinical environments. Two therapists are present throughout to offer guidance and support as needed, but study participants are encouraged to wear an eye mask, to listen to music, and to focus inwardly. Published guidelines suggest that one benefit of having two therapists present is that the participant will not be left alone if one therapist has to leave the room (Johnson et al. 2008). This practice also helps prevent inappropriate boundary crossing or sexual relationships between therapists and patients, which was occasionally problematic during use of MDMA in therapy in the 1980s (Passie 2018). The music used varies, but often emphasizes instrumental, atmospheric songs (Davis et al. 2020; Carhart-Harris et al. 2016a). After dosing, additional sessions with study therapists allow subjects to discuss their experiences. Most studies have used individualized preparatory and integration therapy, though one study used group therapy (Anderson et al. 2020a). Whereas the therapy approach in most studies could be described as supportive psychotherapy, some studies have used manual-based psychotherapies including cognitive-behavioral therapy and motivational enhancement therapy for treatment of addictive disorders (Bogenschutz et al. 2015; Johnson et al. 2014).

While there is general consensus on the importance of maximizing a sense of psychological safety during psychedelic treatment, precisely how much psychological support is necessary and what types of supporting therapies and settings might optimize outcomes for specific populations are subjects for further research. Combining medication with psychological guidance offers more flexibility in treatment approach, but also complicates the assessment of any intrinsic therapeutic efficacy of the drugs.

Challenges of placebo control and expectancy effects

The marked psychological effects of classical psychedelics make blinding difficult in placebo-controlled studies. Given the importance of set and setting, expectations of study participants and staff likely affect the nature of the experience,

leading to challenges in identifying drug-specific effects (Muthukumaraswamy et al. 2021). The underlying concept of the efficacy of pharmacotherapy as distinguished from placebo effect and psychotherapeutic intervention is itself problematic in this field, given the challenges of blinding and the likely importance of psychological framing of psychedelic experiences in treatment outcomes (Gukasyan and Nayak 2021). It is unclear how recent widespread media coverage of psychedelics including may affect expectancy about psychedelic treatments.

Many recent studies have had open-label designs (Table 1). Randomized, placebo-controlled studies have mostly used active placebos, including niacin, low-dose psychedelic, and methylphenidate (Table 1). Niacin has been ineffective as an active placebo, with study staff correctly guessing treatment condition in 97% of cases in one study (Ross et al. 2016), and another study reporting that treatment condition was almost always apparent to both investigators and participants (Grob et al. 2011). In a study comparing low-dose (20 mcg) to high-dose (200 mcg) LSD, 100% of participants and 96% of therapists correctly guessed treatment assignment (Gasser et al. 2015). Two studies using low-dose psilocybin (1 mg) as a control were modestly more effective in maintaining blinding (Griffiths et al. 2016; Griffiths et al. 2018): lead investigators were intentionally vague about experimental protocol to participants and therapists, stating that psilocybin would be given but might be at a variety of doses, leading to misperceptions among study staff and subjects about exact dosing. Methylphenidate had limited success maintaining blind, with 23% of sessions misclassified by study therapists (Griffiths et al. 2006).

Rather than using active placebo, a recent study of psilocybin for depression used a single-blind method with patients randomized to immediate or delayed treatment, with clinical raters blinded to treatment arm (Davis et al. 2020). Though this strategy minimizes expectancy effects for raters, it cannot minimize expectancy effects of participants or therapists.

Psychedelic treatments raise complex questions regarding scientific validity and clinical efficacy. While expectancy effects could be minimized by not informing participants what drugs they might receive and potential effects, this raises ethical concerns and may unacceptably increase participants' psychological risk. A version of this approach, which involved telling participants they might receive a variety of drugs including the actual drug being tested, has been applied in ketamine research (Dakwar et al. 2019). Minimizing concrete information offered about study protocol to therapists and participants or providing ambiguous information may help preserve some degree of blind. Active placebos may assist to some degree in preserving blind but have had limited success in prior trials reporting on this outcome. Avoiding enrolling subjects with prior psychedelics exposure may improve blinding. Assessing pre-treatment expectations and aspects of set and setting (e.g., quality of the therapeutic relationship), and the relationship of these variables to outcome, may be useful.

Limited generalizability of existing results

Many potential participants have been screened out of recent studies (Table 1), which have involved racially homogeneous, highly educated treatment populations. While other populations may benefit from psychedelic therapy, personal and cultural openness to the treatment model may impact clinical outcomes.

A commonly used exclusion criterion is a perceived inability to establish rapport with the treatment team, such as individuals with suspected borderline personality disorder (BPD) (Carhart-Harris et al. 2018b). In a recent study of psilocybin therapy for MDD, 24% of patients brought in for in-person screening were excluded due to this diagnosis (Davis et al. 2020). Several patients with diagnosed BPD were included in another recent study; while noted to have challenging treatments, most benefitted from participation (Anderson et al. 2020a). The feasibility and efficacy of psychedelic therapy for patients with comorbid personality disorders remains unclear.

Treatment efficacy

Several recent psychedelic studies have demonstrated evidence of rapid-acting and often sustained benefits from a small number of treatments (Table 1).

Major depressive disorder

Carhart-Harris et al. (2016a, 2018b) conducted an open-label study in which 20 patients with treatment-resistant depression were treated with two doses of psilocybin (10 mg and 25 mg), spaced 1 week apart. Eighteen of 20 patients met criteria for severe depression at baseline (Quick Inventory of Depression Symptoms QIDS-SR16 $\geq$ 16) and two met criteria for moderate depression. Participants had a median of 4 ineffective medication trials prior to entering the study. All patients except one were tapered off antidepressant medication prior to the trial. Post-dosing, depressive symptoms measured by QIDS-SR16 were significantly decreased from 1 week to 6 months compared to baseline scores, with a maximum effect size of $d = 2.3$ at 5 weeks which decreased to 1.5 at 3 months. Suicidality scores were significantly reduced at one and two weeks post-treatment. Forty-five percent of patients met criteria for response and 20% for remission at 5 weeks. All patients showed some reduction in depression severity at 1 week. No patients began new treatments within 5 weeks of the 25 mg dose,

but 6 began antidepressant medications after the 3-month time point, and 5 sought and obtained illicit psilocybin.

Davis et al. (2020) conducted a randomized crossover study of psilocybin for MDD. Twenty-seven patients were randomized, and 24 completed treatment. The trial employed a single-blind, waitlist randomization structure in which patients were randomized to either immediate treatment with 20 mg/70 kg and 30 mg/70 kg psilocybin spaced 1 week apart or waitlist followed by treatment. The mean baseline Hamilton Depression (GRID-HAM-D) scores for the group were indicative of moderate to severe depression. Patients were not enrolled if currently taking antidepressant medication. Participants were randomized using urn randomization, balancing for sex, age, depression severity at screening, and level of treatment resistance. The QIDS-SR showed a rapid, large decrease in mean depression score from baseline to day 1 after psilocybin session 1 ($d = 2.6$), which remained through week 4 after session 2 ($d = 2.3$). Pronounced differences between groups in depression symptoms were found at 4 weeks after the immediate treatment group concluded treatment, prior to treatment for the waitlist group ($d = 2.6$). Across all patients, 71% had a clinically significant response to the intervention at both 1 week and 4 weeks after finishing treatment, and 58% and 54% were in remission at these time points, respectively.

Carhart-Harris et al. (2021) performed the first RCT comparing psilocybin-assisted therapy to SSRIs for MDD. Fifty-nine study participants were randomized to either receive two psychedelic doses (25 mg) of psilocybin 3 weeks apart and daily placebo for 6 weeks or two low doses (1 mg) of psilocybin and 6 weeks of escalating doses of escitalopram up to 20 mg. At baseline, depressive symptoms ranged from mild to severe, with most participants in the moderate range. Participants were tapered off all psychiatric medication prior to receiving study treatments. Most participants were self-referred and expressed a preference for psilocybin over escitalopram treatment. All participants were told that they would receive psilocybin in the trial, without specifying dose. The primary outcome, change from baseline in QIDS-SR-16 score 6 weeks after the final psilocybin session, was -8.0 ± 1.0 in the psilocybin group and -6.0 ± 1.0 in the escitalopram group (difference, -2.0; 95% confidence interval [CI], -5.0 to 0.9) indicating no significant difference between trial groups ($P = 0.17$). Treatment response was 70% (21/30) in the psilocybin arm compared to 48% (14/29) of escitalopram-treated subjects (confidence interval -3 to 48). Remission, defined as QIDS score of ≤ 5 at week 6, was noted in 57% (17/30) of psilocybin-treated subjects versus 28% (8/29) of escitalopram-treated subjects (confidence interval 2.3 to 53.8). Most secondary analyses favored psilocybin over escitalopram. Adverse events were similar in both groups, though 17% (5/29) of escitalopram-treated participants either intentionally reduced dose or discontinued use in response to perceived side effects, while none discontinued treatment in the psilocybin arm (e.g., by not receiving both doses). This study did not consider acute dysphoria in response to treatment as an adverse event.

Several recent studies have used ayahuasca in treatment of major depression. An open-label study treated 17 participants with 120–200 mL of ayahuasca after initial 2-week inpatient hospitalization (Osorio Fde et al. 2015; Sanches et al. 2016). Unlike other studies, patients were allowed to sit alone in a comfortable room for most of the treatment session. Average baseline HAM-D scores were 17.56 and 19.24. Treatment produced rapid decreases in symptoms that were sustained at 3 weeks.

A placebo-controlled study randomized 29 patients with treatment-resistant depression (mean HAM-D = 21.38) to receive ayahuasca (0.36 mg/kg N, N-DMT) or placebo after a 2-week inpatient hospitalization (Palhano-Fontes et al. 2019). Substantial decreases in HAM-D scores were noted in the treatment group 1 week following treatment ($d = 2.22$), with a between-group effect size of $d = 0.98$. Forty-three percent of patients in the treatment group were in remission at 1 week compared to 13% in the placebo group, which was not significant. Only 1 week of follow-up was available. Placebo response was high 1 day after treatment, with 46% of patients receiving placebo responding based on MADRS scores.

Severe medical condition-related anxiety and mood disorders

Several recent studies have used psychedelics to alleviate anxiety, depression, and existential distress related to severe illness. Grob et al. (2011) conducted a randomized, double-blind crossover study on 12 subjects with advanced-stage cancer and diagnoses of acute stress disorder, generalized anxiety disorder (GAD), anxiety disorder due to cancer, or adjustment disorder with anxiety. Participants received either 0.2 mg/kg psilocybin or niacin on two dates several weeks apart. State-Trait Anxiety Inventory (STAI) scores had no significant changes from 1 day to 2 weeks after treatment but reached significance at 1 month and 3 months after the crossover. There was an insignificant trend toward improvement on the Beck Depression Inventory (BDI) scores in the treatment group from 1 day to 2 weeks after treatment which was not seen in the placebo group, while a statistically significant decrease in BDI scores were seen across the entire group 1 month after the second treatment. The authors suggested that larger sample sizes and higher doses may lead to more significant results.

Gasser et al. (Gasser et al. 2015) evaluated the use of LSD for treatment of anxiety related to life-threatening diseases in 12 patients, with half of subjects meeting criteria for GAD. Most participants had malignancies, but several had

autoimmune diseases or chronic neurological conditions. STAI state or trait scores > 40 were required for participation. Participants were randomized to receive 2 sessions of high-dose 200 mcg LSD or two sessions with low-dose 20 mcg LSD, and the group in the low-dose arm was offered open-label treatment with high-dose LSD after 2-month follow-up. STAI Trait Anxiety was significantly lower at 2-month follow-up with an effect size of 1.1, which persisted at 12 months. Three of eight participants in the active treatment arm dropped lower than the threshold score of 40 at 2 months.

Griffiths et al. (Griffiths et al. 2016) conducted a randomized, double-blind crossover study of psilocybin for treatment of cancer-related depression and anxiety. Fifty-six patients with various conditions (DSM-IV diagnosed chronic adjustment disorder with anxiety, chronic adjustment disorder with mixed anxiety and depressed mood, dysthymic disorder, GAD, MDD) were randomized to receive either high-dose (22 mg/70 kg or 30 mg/70 kg) or low-dose (1 mg/70 kg or 3 mg/70 kg) psilocybin, and data from 51 patients were considered suitable for analysis. Fifty-one percent of study participants had previously received psychiatric medication for mood or anxiety symptoms, and baseline GRID-HAM-D scores were suggestive of moderate depression. For depression symptoms, 92% of patients in the treatment group responded to treatment and 60% were in remission 5 weeks following treatment ($p < 0.001$), compared to 32% and 16% in the active placebo group. For anxiety symptoms (HAM-A), 76% responded to treatment and 52% were in remission at 5 weeks, compared to 24% and 12% in the active-placebo group ($p < 0.001$). For all patients at 6 months after completing both treatments, the rate of clinical response was 78% for depression symptoms and 83% for anxiety, with remission rates of 65% and 57%. MEQ scores conducted immediately after sessions correlated with clinical improvements. Blinded community observers rated participants for prosocial behavior (e.g., patience, good-natured humor, optimism, mental flexibility), scores for which were significantly increased from baseline 5 weeks after both treatment sessions.

Ross et al. (Ross et al. 2016) conducted a randomized, double-blind crossover study of psilocybin for treatment of cancer-related anxiety or depression. Ninety percent (26/29) of patients met DSM-IV criteria for cancer-related adjustment disorder with anxious/depressed features. Baseline symptoms were suggestive of mild depression and mild-moderate anxiety. Fifty-five percent of patients had prior experience with psychedelics, but no relationship was found between prior psychedelic use and treatment outcome. Thirty-one patients were randomized to initially receive either 0.3 mg/kg psilocybin or niacin, and 29 patients proceeded with at least one treatment session. Primary outcome measures included Hospital Anxiety and Depression (HADS) Scales (HADS-A, HADS-D, HADS-T), the BDI, and STAI anxiety. Significant differences in all primary outcome measures were found between treatment and the placebo groups beginning day 1 post-dose 1 up to 7 weeks post-dose 1, with effect sizes ranging from $d = 0.82$ to $d = 1.36$. Eighty-three percent of participants in the psilocybin group met criteria for antidepressant response on the BDI versus 14% in the niacin group. Fifty-eight percent met criteria for anxiolytic response on the HADS-A in the psilocybin group versus 14% in the niacin group. At 6.5 months follow-up following the crossover, 23/29 patients provided follow-up data, and antidepressant and anxiolytic responses ranged from 60 to 80% within this group. MEQ scores immediately after dosing were significantly correlated with changes for 4 of 6 primary outcome measures. Eighty-seven percent of participants endorsed increased life satisfaction or well-being related to the experience.

Anderson et al. (2020a) conducted an open-label study of 18 participants using psilocybin with preparatory group therapy for treatment of demoralization related to chronic HIV infection among self-identified gay men over the age of 50. Participants had heterogeneous psychiatric conditions, including GAD, MDD, panic disorder, and BPD. The mean number of prior uses of classical psychedelics in the group was 5, though no correlation was found between prior psychedelic use and treatment outcome. Study participants underwent several hours of individual therapy, 12–15 h of group therapy, and 1 individual psilocybin session with a dose of either 0.3 mg/kg or 0.36 mg/kg. The primary clinical outcome of demoralization showed improvement from baseline to end of treatment and at 3-month follow-up, with an effect size $d_{rm} = 0.97$. At the end of treatment, 50% had a > 50% improvement in demoralization, and 33.3% showed a > 50% decline after 3 months. Patients also showed improvements in metrics of PTSD (PCL-5, ηp2 = 0·27, 90% CI 0.05–0.43) and complicated grief (ICG-R, ηp2 = 0.45, 90% CI 0.19–0.58).

Substance use disorders

Johnson et al. (2014, 2017) studied the effects of psilocybin-assisted therapy for tobacco addiction. Fifteen psychiatrically healthy smokers (mean of 19 cigarettes/day, 6 prior quit attempts) received up to 3 open-label doses of psilocybin (20 mg/70 kg or 30 mg/70 kg), accompanied by cognitive behavioral therapy (CBT) related to smoking cessation and other psychological support, including 5-min phone calls for 2 weeks after initial smoking cessation. Biomarkers (exhaled CO, urine cotinine) were used to measure abstinence in addition to participant reports. A Target Quit Date was set for the day of the first psilocybin session, and 12/15 participants completed 3 psilocybin sessions. Eighty percent of participants showed 7-day point prevalence abstinence at

6-month follow-up, with 4 participants having self-corrected lapses after initial quit dates. At 12-month follow-up, 67% were confirmed abstinent, and 60% were confirmed abstinent at 16 + month follow-up. Over 50% of participants endorsed that psilocybin caused them to quit by (1) changing their value system, (2) reframing quitting as a spiritual task, (3) changing their orientation to the future, and (4) strengthening beliefs in their ability to remain abstinent.

Bogenschutz et al. (2015) studied open-label psilocybin-assisted therapy in treatment of alcohol dependence. Ten participants with DSM-IV diagnosed alcohol dependence received 1–2 doses of psilocybin (0.3 or 0.4 mg/kg) in addition to motivational enhancement therapy (MET), and 9 completed all study assessments. Eighty percent of participants had physical signs of tolerance or withdrawal during the trial, but none had withdrawal symptoms requiring medical care. Participants were required to be abstinent for 24 h without signs of withdrawal at the time of psilocybin administration. Outcome measures included percent drinking days and percent heavy drinking days. No biological verification of drinking was used as an outcome measure, though BACs were taken at study visits to help verify participant-reported drinking metrics. Following initial psilocybin treatment session, percent heavy drinking days and percent drinking days were significantly lower than baseline at all follow-up points, with effect sizes ranging from $d = 0.75–1.38$. Substantial variability in response to psilocybin was observed across participants. Changes in drinking days were highly correlated to subjective ratings of the experience immediately following treatment,.

Dosing

Pharmacologic dosing for psychedelics involves a distinct set of concerns compared to pharmacologic management of typical antidepressant medications. This section focuses on dosing for psilocybin, which most recent clinical studies have used.

Since several studies have correlated ratings of intensity of positively valenced subjective experience to sustained therapeutic effects (Griffiths et al. 2016; Ross et al. 2016; Davis et al. 2020; Garcia-Romeu et al. 2014; Roseman et al. 2017; Bogenschutz et al. 2015), one aspect to consider when choosing dose is the likelihood of inducing such an experience. A dose-finding study in healthy participants found correlations between dose and probability of having a "complete" mystical-type experience as measured by the MEQ (i.e., greater than 60% on each mystical experience subscale), with 0, 5.6, 11.1, 44.4, and 55.6% experiencing complete mystical-type experiences at 0, 0.07, 0.14, 0.29, and 0.43 mg/kg doses, respectively (Griffiths et al. 2011), and another study finding 0%, 20%, and 40% rates of complete mystical-type experiences at 0.14, 0.29, and 0.43 mg/kg in a population experienced with psychedelic use (Carbonaro et al. 2018). However, another study found no relationship between dose and rate of mystical-type experience at 0.3 mg/kg, 0.45 mg/kg, and 0.6 mg/kg, suggesting a potential ceiling effect at higher doses (Brown et al. 2017). Intensity of dysphoric effects is also correlated with dose (Griffiths et al. 2011; Studerus et al. 2011). Notably, healthy volunteers receiving psilocybin in a dose-escalation study rated more substantial mood improvement following treatment as dose increased, whereas this effect was not observed in those receiving doses in descending fashion. Study authors suggested that initial experiences with lower doses of psilocybin may facilitate better experiences at higher doses due to greater familiarity with altered states prior to more intense high-dose experiences (Griffiths et al. 2011). The high dose (0.43 mg/kg) used initially in a study of psilocybin for cancer-related distress was lowered to 0.29 mg/kg after 2 of the first 3 participants left the study following the initial treatment, reported as due to vomiting and personal reasons respectively (Griffiths et al. 2016).

Limited data are available from clinical studies with psychiatrically ill populations to determine optimal dosing, including how many acute treatments are needed at attain treatment response. Two open-label studies of psilocybin for MDD used an escalating dose, two-treatment strategy within 1 week of each other, with one study giving 10 mg and 25 mg (~0.14 mg/kg and 0.35 mg/kg for a 70 kg person) (Carhart-Harris et al. 2016a) and the other giving 0.29 mg/kg and 0.43 mg/kg in succession (Davis et al. 2020); a third treated with 25 mg on two occasions 3 weeks apart (Carhart-Harris et al. 2021). In all three studies that used two treatments, improvement in symptoms appeared to be substantial after the initial dosing, so the importance of an acute two-dose strategy is unclear. In studies using psilocybin for treatment of cancer-related distress, a small study using a single 0.2 mg/kg dose resulted in only mild to moderate improvement (Grob et al. 2011), while studies of similar patient populations using single higher doses (~0.3 mg/kg) resulted in more substantial clinical improvement (Griffiths et al. 2016; Ross et al. 2016).

Dosing schedules of recent studies are summarized in Table 1. Existing data suggest that higher doses up to 0.43 mg/kg psilocybin may have more substantial therapeutic effects, but also cause more intense dysphoria, which may not be well tolerated in some populations. An escalating dose schedule may be optimal if higher doses of up to 0.43 mg/kg are being used. Considering available data, ~0.3 mg/kg is a reasonable psilocybin dose to use for either single treatment or initial treatment in a multi-dose study. Whether multiple treatments within a brief period produce more substantial or sustained therapeutic effects compared to a single treatment remains unclear. Optimal dosing may also vary by treatment population, with some patients

with alcohol dependence having limited responses even to high dose (0.4 mg/kg) psilocybin (Bogenschutz et al. 2015).

Dosing may be impacted for patients currently taking psychiatric medication, with evidence suggesting that chronic administration of various psychiatric medications may attenuate (SSRIs and MAOIs) or intensify (lithium and TCAs) the effects of classical psychedelics (Bonson et al. 1996; Bonson and Murphy 1996). A recent study concluded that benefits of weight-based dosing over fixed dosing may not outweigh the costs (Garcia-Romeu et al. 2021).

Mechanisms

Theories concerning the mechanism of action of psychedelic compounds are multifaceted due to numerous functional levels at which this question can be analyzed. This section offers a brief introduction to several perspectives regarding the theoretical bases for the therapeutic application of psychedelic compounds.

A commonly referenced overarching mechanistic neurobiological principle is that psychedelic compounds act as psychoplastogens (Olson 2021), as potentiators of temporary neuroplasticity which can cause lasting alterations to neural pathways even after limited exposure. Support for this hypothesis can be found in both animal studies and human functional neuroimaging studies (Vaidya et al. 1997; Ly et al. 2018; Jones et al. 2009; Carhart-Harris et al. 2017; Roseman et al. 2018; Barrett et al. 2020). The neurobiological pathway most likely to be important in mediating the initial stages of these changes is agonism of $5HT_{2A}$ serotonin receptors, which has been demonstrated to be necessary for characteristic psychological effects of psychedelic drugs (Vollenweider et al. 1998; Preller et al. 2017) as well as neural growth in animal models (Vaidya et al. 1997; Ly et al. 2018). The $5HT_{2A}$ receptor is an excitatory receptor situated predominantly on cortical neurons. Its highest concentrations are in areas crucial for high-level sensory processing, cognition, and mood regulation, including the brain's default mode network (DMN), salience network, and executive network (Nichols 2016; Carhart-Harris and Nutt 2017).

Though $5HT_{2A}$ receptor agonism is necessary to induce full psychedelic experiences, classical psychedelics act at numerous other receptors, including predominantly inhibitory $5HT_{1A}$ serotonin receptors. Agonism at $5HT_{1A}$ may also mediate antidepressant effects, as demonstrated by a recent animal study (Hesselgrave et al. 2021), though these antidepressant mechanisms are likely distinct from those related to $5HT_{2A}$ agonism (Carhart-Harris and Nutt 2017). In humans, concomitant treatment with the $5HT_{1A}$ agonist buspirone has been demonstrated to decrease certain subjective effects of psilocybin (Pokorny et al. 2016), while combined treatment with the serotonergic psychedelic dimethyltryptamine and the functional $5HT_{1A}$ antagonist pindolol led to increased subjective effects (Strassman 1996), suggesting that these receptors are playing distinct and plausibly oppositional roles (Carhart-Harris and Nutt 2017). Recently, researchers have developed $5HT_{2A}$ agonists that appear not to cause psychedelic effects in animal models (Cameron et al. 2021), though there are no data that they do not cause subjective effects in humans, or that they will be efficacious treatments of psychiatric disorders.

Due to the marked and variable psychological effects of psychedelic compounds, it has been hypothesized that the nature of the subjective experience plays an important role in treatment efficacy. During the first wave of clinical psychedelic research, psychedelic use to catalyze psychoanalysis (the psycholytic paradigm) was contrasted with the "psychedelic" paradigm, in which high doses of drug were used to induce an inwardly directed, transformative experience (Grinspoon and Bakalar 1979). Recent studies more closely resemble the latter paradigm, discouraging much active engagement with therapists during peak drug effects. An influential study found that administration of psilocybin in a controlled setting induced a full mystical-type experience in 61% of healthy volunteers (Griffiths et al. 2006). The importance of the "mystical experience" in therapeutic outcomes continues to be debated (Olson 2021; Yaden and Griffiths 2021). Correlations between sustained reduction in symptoms and MEQ scores immediately following treatment suggest that subjective experiences play a significant role in treatment efficacy across diagnostic categories, though observed correlations may not necessarily be indicative of a causal relationship.

Recent neuroimaging studies demonstrated decreases in brain DMN connectivity during treatment with both psilocybin and LSD, which correlated with subjective drug effects (Carhart-Harris et al. 2012, 2016b). These findings contributed to the development of a novel theory of mechanism of action advanced by Robin Carhart-Harris (Carhart-Harris et al. 2014), which postulates that the DMN is a neural representation of the "ego" or "narrative self" that integrates sensory inputs with memory to produce behavior. Its roles include dictating the salience of sensory events and constraining perception in accordance with prior learning. Carhart-Harris argues that this constraining function can be either useful or maladaptive depending on the utility of existing neural architecture for navigating present environments. Psychedelic drugs have the potential to temporarily, but dramatically, alter existing connections within the DMN, leading to a less constrained mode of cognition. This induces significant changes in neural architecture and psychological outlook, with some studies even finding personality changes after psychedelic use (Bouso et al. 2018). For this reason, psychiatric disorders that are characterized by excessive rigidity of thought and behavior—including mood, anxiety, obsessive–compulsive, eating, and substance

use disorders—might be amenable to treatment with psychedelics (Carhart-Harris et al. 2014).

Discussion

Over the past decade, the application of psychedelic drugs for therapeutic purposes has evolved from a fringe pursuit of a small number of research groups to a topic of broad scientific inquiry. MDMA, a mind-altering amphetamine derivative with psychedelic properties (though not a classical psychedelic), may be legalized as a psychiatric treatment as soon as 2023, and the classical psychedelic psilocybin may soon follow. Numerous other psychedelics are being studied. Among the public, psychedelic drugs have shifted from being perceived as drugs of abuse to being regarded more ambivalently, as potentially important medicines or even as a panacea for broader social problems. This cultural evolution has reached the point that prominent researchers have begun to publicly emphasize potential risks rather than primarily advocating for these experimental treatments (Yaden et al. 2021; Anderson et al. 2020b).

Given this evolving scientific and cultural landscape, it is important to understand the available data, particularly from recent studies using contemporary methods. Therapeutic efficacy has been rapid in onset, even among patient populations with significant mental illness. Effect sizes for several studies have been large, with psychedelic treatment bringing remission of even longstanding, treatment-resistant disorders. The adverse effect profile for carefully screened populations in controlled settings has generally been benign, with most adverse effects limited to the day of dosing, suggesting that these treatments may be desirable options even for those with mild to moderate symptoms.

Enthusiasm should be tempered in several respects. Recent psychedelic clinical literature is growing but remains limited in total patient enrollment. As noted above, the post-1991 published psychedelic literature consists of only fourteen clinical trials, reporting on 315 patients. When published, results of Phase 2b studies (Compass Pathways, $N=216$, and Usona Foundation, $N=80$) will more than double the available data on psychedelic treatment of MDD. Other ongoing studies will contribute additional data.

The view that classical psychedelics could serve as a "cure" for chronic mental illness is not empirically supported. While those treated for adjustment or mood disorders related to serious medical diagnoses often experienced lasting benefits, existing studies of major depression demonstrate sustained improvements for weeks or months that gradually diminish in magnitude, or they have not reported on long-term follow-up.

Psychedelic treatments have not been demonstrated to be superior to existing pharmacologic treatments, with a recent RCT not finding superior efficacy of psilocybin to escitalopram (Carhart-Harris et al. 2021). While it should be noted that secondary measures largely favored psilocybin, the study was not powered to demonstrate the superiority of one treatment over another. Perhaps more important to emphasize is that psychedelic therapy offers a treatment paradigm distinct from traditional pharmacologic treatment, in which relatively few doses of a psychoactive drug, in combination with supportive therapy, may lead to lasting change. Psychological effects differ dramatically from those of current antidepressants: rather than emotional blunting or apathy often experienced with SSRIs (Goodwin et al. 2017), patients receiving psilocybin commonly report benefits such as an increased ability to feel strong emotions, which may be related to fundamental neurobiological mechanisms of each drug class (Watts et al. 2017; Carhart-Harris et al. 2021; Carhart-Harris and Nutt 2017). Experiences of emotional confrontation and catharsis which seem to characterize psychedelic therapies may be preferable to sustained medication use for some patients.

For the past 50 years, psychedelics have been construed as dangerous drugs of abuse. Recent data have clarified this risk profile. From recent study reports, it appears that no significant physiologic harm or hospitalizations have occurred during more than two thousand dosing sessions. While acute psychological instability has been commonly observed, sustained psychological instability has been rare and limited in severity. No serious, lasting psychiatric consequences attributed to psychedelics are reported among participants in post-1991 research studies through mid-2021.

While these results are promising, important qualifications should be noted. Data were collected from highly screened research populations, which exclude many individuals potentially at increased risk for adverse outcomes. Risks are likely greater in settings with less rigorous screening of patients or training and supervision of providers. Broader implementation will require the development of appropriate ethical guidelines, robust provider training programs, and regulatory structures to prevent misuse of psychedelic treatments. Initiatives to decriminalize or legalize psychedelic drugs as being pursued in Oregon, could expose vulnerable individuals to significant risks.

Many scientific and clinical questions require future research. In addition to demonstrating efficacy for treatment of depression in larger, multisite clinical trials, other conditions—such as substance use disorders, anxiety disorders, PTSD, eating disorders, and chronic pain disorders—warrant further study. Comparative efficacy studies can establish which disorders respond best to which psychedelic treatments.

There are no data regarding best practices for maintaining remission after initial improvements, which could include use of traditional antidepressants, brain stimulation, repeated

psychedelic dosing, psychedelic microdoses, or other options. Over time, assuming positive findings from ongoing clinical trials, more detailed dosing protocols can be developed for various conditions. Studies assessing the safety, efficacy, and dosing of psychedelic treatments for individuals taking other psychiatric medications, such as SSRIs, are highly relevant to clinical implementation. Studies assessing the comparative efficacy of various accompanying psychotherapy approaches may also be beneficial.

It is important to emphasize how different psychedelic treatments are from traditional pharmacotherapies. Psychedelic treatments in studies to date are combined treatments, encompassing medication and psychotherapy, in which patient experiences can be remarkably intense and unpredictable. It is often ambiguous whether a patient's acute response to a psychedelic should be considered normal or an adverse event, and as such, the definition of and reporting on adverse events for psychedelic treatments is variable in the literature. The intensity of psychedelic experiences leads to unique difficulties in conducting placebo-controlled studies. The importance of set and setting to the subjective experience—and likely to therapeutic efficacy and adverse experiences—leads to further complexity in evaluating treatment safety and efficacy.

Best practices concerning placebo control and managing expectancy effects remain controversial. On one side of the spectrum, one might argue that developing methods to enable effective placebo control, and to prevent participants from ascertaining that they are receiving active treatment, is necessary for establishing the scientific legitimacy of psychedelics. This might be achieved by providing minimal information about compounds being offered, finding better active placebos, excluding participants with previous psychedelic experience, and using study designs that do not directly inform participants of the drug being studied (Dakwar et al. 2019).

However, there is reason to believe that such efforts will inevitably be limited, and arguably misguided in psychedelic-assisted therapy. Classical psychedelics have been characterized as "meaning-response magnifiers" or "amplifiers of consciousness" (Hartogsohn 2016). From this perspective, the compounds might serve many potential social roles: healing, if taken for the express purpose of healing in a comfortable or inspiring milieu, or punishment, if given when an individual is not psychologically prepared or the drug is administered in an adverse environment. Cultures with socially approved uses of psychedelic plants have developed complex narratives and rituals surrounding their use, intentionally priming users for jointly desired experiences (Schultes et al. 2001; Myerhoff 1974; Fernandez 2019). Attempting to minimize expectancy effects could compromise therapeutic action and even increase adverse events, especially if this approach leads participants to mistrust study staff. A corollary of this premise is that framing the psychedelic experience in particular ways—e.g., as a means to achieve transformative mystical experiences, or as chemical catalysts for resetting the brain's default mode network—may carry their own benefits and risks.

The set and setting of participating in a placebo-controlled trial may themselves affect efficacy for both treatment and placebo groups. A participant randomized to receive placebo may correctly guess treatment assignment and may feel disappointment and frustration. This would diverge from anticipated placebo responses, which would generally involve some benefit, though to a lesser degree than active treatment. The case of a study participant in a study of psilocybin-assisted therapy for depression and anxiety related to life-threatening cancer is pertinent. Having received low-dose or "placebo" dose psilocybin, the participant grew bored during the treatment session. He chose to leave early, and dropped out of the study. He committed suicide 11 days later. This was not attributed to the placebo-level dose of psilocybin itself (Griffiths et al. 2016) but could be understood as a sort of nocebo response.

Clinical researchers should therefore be particularly conscious of these issues while planning psychedelic studies. Methods used to frame the intent of treatment to study participants and staff should be considered part of the intervention, and carefully documented. Expectancy effects can be quantitatively measured by scales like the Credibility and Expectancy Questionnaire or the Stanford Expectations of Treatment scale. Measuring traits of participants such as suggestibility or hypnotizability may offer additional valuable data. Qualitative and quantitative data on participant reactions to ways in which the treatment method is presented, and the setting of treatment, may also be valuable. This might involve the following: collecting data on how participants felt about undergoing treatment in a psychiatric hospital; their assessment of the purpose of psychedelic therapy at beginning and end of the study; reactions to music playlists; or innumerable other ways of understanding patient experiences. The Working Alliance Inventory and the Barrett-Lenard Relationship Inventory can inform how treatment alliance affects outcomes. Researchers planning placebo-controlled studies should appreciate the challenges that prior studies have faced in concealment, and either attempt novel approaches to improve blinding or opt for other study designs, depending on the goals of a given study, e.g., with waitlist control or open-label design.

Limitations

This review has several limitations. A wealth of early clinical literature from the 1950s to 1960s was not highlighted. Because the timeframe for review is only through June 2021, results from the as yet unpublished Compass Pathways Phase

IIb trial were not considered in the review. The heterogeneity of methods and treatment populations among studies reviewed, including data reported by various investigators—e.g., rates and types of acute adverse psychological events—hindered the ability to compile certain endpoints of interest or perform meta-analysis. Few clinical trials have been performed on classical psychedelic drugs other than psilocybin since 1991, so this review largely focuses on this compound. Therefore, conclusions may not be broadly applicable—e.g., regarding dosing—or generalizable to other classical psychedelics. Though systematic review methods were used to ensure the inclusion and analysis of all clinical trial data on classical psychedelics, this review drew on numerous other sources of information in addition to the systematic search, and references chosen are susceptible to reviewer bias.

Conclusions

Substantial progress has been made toward establishing the efficacy of psychedelic-assisted psychotherapy in the treatment of various psychiatric conditions. Clinical studies with psychedelic compounds raise complex scientific challenges, particularly around treatment blinding, placebo control, and the role of set and setting, and may require innovative changes to study design. While psychedelics' safety profile appears promising on the basis on existing studies, results may not be generalizable, particularly if drugs are administered by inexperienced or improperly trained providers to more varied and vulnerable clinical populations. Clinical researchers should take these methodological issues into account when planning future studies, and policymakers should recognize the unique set of risks when considering socially sanctioned use of these compounds.

Declarations

Conflict of interest DB: no conflicts. DH: Dr. Hellerstein has received research funding support from Compass Pathways for psilocybin studies and from Pfizer, Lilly, Takeda, GeneSight, Marinus, Relmada, and IntraCellular Therapies for other studies. He is on the scientific advisory board for Reset Pharmaceuticals.

References

Aakeroy R et al (2020) Severe neurological sequelae after a recreational dose of LSD. J Anal Toxicol 45(7):e1–e3

Abramson HA et al (1957) Production of tolerance to psychosis-producing doses of lysergic acid diethylamide. Science 126(3281):1020

Aday JS et al (2021) Predicting reactions to psychedelic drugs: a systematic review of states and traits related to acute drug effects. ACS Pharmacol Transl Sci 4(2):424–435

Andersen KAA et al (2021) Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. Acta Psychiatr Scand 143(2):101–118

Anderson BT et al (2020a) Psilocybin-assisted group therapy for demoralized older long-term AIDS survivor men: An open-label safety and feasibility pilot study. EClinicalMedicine 27:100538

Anderson BT, Danforth AL, Grob CS (2020b) Psychedelic medicine: safety and ethical concerns. Lancet Psychiatry 7(10):829–830

Barrett FS et al (2016) The Challenging Experience Questionnaire: Characterization of challenging experiences with psilocybin mushrooms. J Psychopharmacol 30(12):1279–1295

Barrett FS et al (2020) Emotions and brain function are altered up to one month after a single high dose of psilocybin. Sci Rep 10(1):2214

Belser AB, Agin-Liebes G, Swift TC, Terrana S, Devenot N, Friedman HL, Guss J, Bossis A, Ross S (2017) Patient experiences of psilocybin-assisted psychotherapy: an interpretative phenomenological analysis. J Humanist Psychol 57:354–388

Berrens Z, Lammers J, White C (2010) Rhabdomyolysis after LSD ingestion. Psychosomatics 51(4):356-3563 e3

Bickel M et al (2005) Severe rhabdomyolysis, acute renal failure and posterior encephalopathy after "magic mushroom" abuse. Eur J Emerg Med 12(6):306–308

Bogenschutz MP et al (2015) Psilocybin-assisted treatment for alcohol dependence: a proof-of-concept study. J Psychopharmacol 29(3):289–299

Bogenschutz MP et al (2018) Clinical interpretations of patient experience in a trial of psilocybin-assisted psychotherapy for alcohol use disorder. Front Pharmacol 9:100

Bonson KR, Murphy DL (1996) Alterations in responses to LSD in humans associated with chronic administration of tricyclic antidepressants, monoamine oxidase inhibitors or lithium. Behav Brain Res 73(1–2):229–233

Bonson KR, Buckholtz JW, Murphy DL (1996) Chronic administration of serotonergic antidepressants attenuates the subjective effects of LSD in humans. Neuropsychopharmacology 14(6):425–436

Borowiak KS, Ciechanowski K, Waloszczyk P (1998) Psilocybin mushroom (Psilocybe semilanceata) intoxication with myocardial infarction. J Toxicol Clin Toxicol 36(1–2):47–49

Bouso JC et al (2012) Personality, psychopathology, life attitudes and neuropsychological performance among ritual users of Ayahuasca: a longitudinal study. PLoS One 7(8):e42421

Bouso JC et al (2018) Serotonergic psychedelics and personality: A systematic review of contemporary research. Neurosci Biobehav Rev 87:118–132

Brown RT et al (2017) Pharmacokinetics of escalating doses of oral psilocybin in healthy adults. Clin Pharmacokinet 56(12):1543–1554

Buckholtz NS et al (1990) Lysergic acid diethylamide (LSD) administration selectively downregulates serotonin2 receptors in rat brain. Neuropsychopharmacology 3(2):137–148

Cameron LP et al (2021) A non-hallucinogenic psychedelic analogue with therapeutic potential. Nature 589(7842):474–479

Carbonaro TM et al (2016) Survey study of challenging experiences after ingesting psilocybin mushrooms: Acute and enduring positive and negative consequences. J Psychopharmacol 30(12):1268–1278

Carbonaro TM et al (2018) Double-blind comparison of the two hallucinogens psilocybin and dextromethorphan: similarities and differences in subjective experiences. Psychopharmacology 235(2):521–534

Carhart-Harris RL, Nutt DJ (2017) Serotonin and brain function: a tale of two receptors. J Psychopharmacol 31(9):1091–1120

Carhart-Harris RL et al (2012) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. Proc Natl Acad Sci U S A 109(6):2138–2143

Carhart-Harris RL et al (2014) The entropic brain: a theory of conscious states informed by neuroimaging research with psychedelic drugs. Front Hum Neurosci 8:20
Carhart-Harris RL et al (2016a) Psilocybin with psychological support for treatment-resistant depression: an open-label feasibility study. Lancet Psychiatry 3(7):619–627
Carhart-Harris RL et al (2016b) Neural correlates of the LSD experience revealed by multimodal neuroimaging. Proc Natl Acad Sci U S A 113(17):4853–4858
Carhart-Harris RL et al (2017) Psilocybin for treatment-resistant depression: fMRI-measured brain mechanisms. Sci Rep 7(1):13187
Carhart-Harris RL et al (2018a) Psychedelics and the essential importance of context. J Psychopharmacol 32(7):725–731
Carhart-Harris RL et al (2018b) Psilocybin with psychological support for treatment-resistant depression: six-month follow-up. Psychopharmacology 235(2):399–408
Carhart-Harris R et al (2021) Trial of psilocybin versus escitalopram for depression. N Engl J Med 384(15):1402–1411
Cerletti AU (1958) Etude pharmacologique de la psilocybine Les champignons hallucinogenes du mexique. Museum de historie naturelle, Paris, pp 268–271
Dahmane E, Hutson PR, Gobburu JVS (2021) Exposure-response analysis to assess the concentration-QTc relationship of psilocybin/psilocin. Clin Pharmacol Drug Dev 10(1):78–85
Dakwar E et al (2019) A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: a randomized clinical trial. Am J Psychiatry 176(11):923–930
Davis AK et al (2020) Effects of psilocybin-assisted therapy on major depressive disorder: a randomized clinical trial. JAMA Psychiatry 78(5):481–489
Dishotsky NI et al (1971) LSD and genetic damage. Science 172(3982):431–440
Fantegrossi WE, Woods JH, Winger G (2004) Transient reinforcing effects of phenylisopropylamine and indolealkylamine hallucinogens in rhesus monkeys. Behav Pharmacol 15(2):149–157
Fernandez JW (2019) Bwiti: an ethnography of the religious imagination in Africa. Princeton University Press
Garcia-Romeu A, Griffiths RR, Johnson MW (2014) Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. Curr Drug Abuse Rev 7(3):157–164
Garcia-Romeu A et al (2019a) Cessation and reduction in alcohol consumption and misuse after psychedelic use. J Psychopharmacol 33(9):1088–1101
Garcia-Romeu A et al (2019b) Persisting Reductions in Cannabis, Opioid, and Stimulant Misuse After Naturalistic Psychedelic Use: An Online Survey. Front Psychiatry 10:955
Garcia-Romeu A et al (2021) Optimal dosing for psilocybin pharmacotherapy: considering weight-adjusted and fixed dosing approaches. J Psychopharmacol 35(4):353–361
Gasser P et al (2014) Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. J Nerv Ment Dis 202(7):513–520
Gasser P, Kirchner K, Passie T (2015) LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. J Psychopharmacol 29(1):57–68
Goodwin GM et al (2017) Emotional blunting with antidepressant treatments: a survey among depressed patients. J Affect Disord 221:31–35
Gresch PJ et al (2005) Behavioral tolerance to lysergic acid diethylamide is associated with reduced serotonin-2A receptor signaling in rat cortex. Neuropsychopharmacology 30(9):1693–1702
Griffiths RR et al (2006) Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl) 187(3):268–83 discussion 284-92
Griffiths RR et al (2011) Psilocybin occasioned mystical-type experiences: immediate and persisting dose-related effects. Psychopharmacology 218(4):649–665
Griffiths RR et al (2016) Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: a randomized double-blind trial. J Psychopharmacol 30(12):1181–1197
Griffiths RR et al (2018) Psilocybin-occasioned mystical-type experience in combination with meditation and other spiritual practices produces enduring positive changes in psychological functioning and in trait measures of prosocial attitudes and behaviors. J Psychopharmacol 32(1):49–69
Griffiths RR, Bigelow GE, Henningfield JE (1980) Similarities in animal and human drug-taking behavior. In: Mello NK (ed) Advances in Substance Abuse. JAI Press Inc, Greenwich, CT, pp 1–90
Grinspoon L, Bakalar JB (1979) Psychedelic drugs reconsidered. Basic Books, New York xiv, 343 p
Grob CS et al (1996) Human psychopharmacology of hoasca, a plant hallucinogen used in ritual context in Brazil. J Nerv Ment Dis 184(2):86–94
Grob CS et al (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. Arch Gen Psychiatry 68(1):71–78
Gukasyan N, Nayak SM (2021) Psychedelics, placebo effects, and set and setting: Insights from common factors theory of psychotherapy. Transcult Psychiatry 26:1363461520983684
Halpern JH, Pope HG Jr (1999) Do hallucinogens cause residual neuropsychological toxicity? Drug Alcohol Depend 53(3):247–256
Halpern JH, Pope HG Jr (2003) Hallucinogen persisting perception disorder: what do we know after 50 years? Drug Alcohol Depend 69(2):109–119
Halpern JH et al (2005) Psychological and cognitive effects of long-term peyote use among Native Americans. Biol Psychiatry 58(8):624–631
Halpern JH, Lerner AG, Passie T (2018) A review of hallucinogen persisting perception disorder (HPPD) and an exploratory study of subjects claiming symptoms of HPPD. Curr Top Behav Neurosci 36:333–360
Hartogsohn I (2016) Set and setting, psychedelics and the placebo response: an extra-pharmacological perspective on psychopharmacology. J Psychopharmacol 30(12):1259–1267
Hasler F et al (2004) Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. Psychopharmacology 172(2):145–156
Heise CW, Brooks DE (2017) Ayahuasca exposure: descriptive analysis of calls to US poison control centers from 2005 to 2015. J Med Toxicol 13(3):245–248
Hendin HM, Penn AD (2021) An episode of mania following self-reported ingestion of psilocybin mushrooms in a woman previously not diagnosed with bipolar disorder: A case report. Bipolar Disord 23(7):733–735
Hendricks PS et al (2015) Classic psychedelic use is associated with reduced psychological distress and suicidality in the United States adult population. J Psychopharmacol 29(3):280–288
Hesselgrave N et al (2021) Harnessing psilocybin: antidepressant-like behavioral and synaptic actions of psilocybin are independent of 5-HT2R activation in mice. Proc Natl Acad Sci U S A 118(17):e2022489118
Holze F et al (2020) Distinct acute effects of LSD, MDMA, and D-amphetamine in healthy subjects. Neuropsychopharmacology 45(3):462–471

Holze F et al (2021) Acute dose-dependent effects of lysergic acid diethylamide in a double blind placebo controlled study in healthy subjects. Neuropsychopharmacology 46(3):537–544 https://reporter.nih.gov/search/_NuFp5PaT0alcI1JOIRGVA/project-details/10127338

Hyde R (1960) Psychological and social determinants of drug action. Dynamics of Psychiatric Drug Therapy. Sarwer-Foner G (ed) Springfield, pp 297–315

Johansen PO, Krebs TS (2015) Psychedelics not linked to mental health problems or suicidal behavior: a population study. J Psychopharmacol 29(3):270–279

Johnson M, Richards W, Griffiths R (2008) Human hallucinogen research: guidelines for safety. J Psychopharmacol 22(6):603–620

Johnson MW, Sewell RA, Griffiths RR (2012) Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. Drug Alcohol Depend 123(1–3):132–140

Johnson MW et al (2014) Pilot study of the 5-HT2AR agonist psilocybin in the treatment of tobacco addiction. J Psychopharmacol 28(11):983–992

Johnson MW, Garcia-Romeu A, Griffiths RR (2017) Long-term follow-up of psilocybin-facilitated smoking cessation. Am J Drug Alcohol Abuse 43(1):55–60

Johnson MW et al (2018) The abuse potential of medical psilocybin according to the 8 factors of the Controlled Substances Act. Neuropharmacology 142:143–166

Jones KA et al (2009) Rapid modulation of spine morphology by the 5-HT2A serotonin receptor through kalirin-7 signaling. Proc Natl Acad Sci U S A 106(46):19575–19580

Krebs TS, Johansen PO (2012) Lysergic acid diethylamide (LSD) for alcoholism: meta-analysis of randomized controlled trials. J Psychopharmacol 26(7):994–1002

Langs RJ, Barr HL (1968) Lysergic acid diethylamide (LSD-25) and schizophrenic reactions. A comparative study. J Nerv Ment Dis 147(2):163–72

Leary T (1964) The psychedelic experience: a manual based on the Tibetan book of the dead. University Books, New York

Leonard JB, Anderson B, Klein-Schwartz W (2018) Does getting high hurt? Characterization of cases of LSD and psilocybin-containing mushroom exposures to national poison centers between 2000 and 2016. J Psychopharmacol 32(12):1286–1294

Liechti ME (2017) Modern Clinical Research on LSD. Neuropsychopharmacology 42(11):2114–2127

Liechti ME, Dolder PC, Schmid Y (2017) Alterations of consciousness and mystical-type experiences after acute LSD in humans. Psychopharmacology (Berl) 234(9–10):1499–1510

Lim TH, Wasywich CA, Ruygrok PN (2012) A fatal case of "magic mushroom" ingestion in a heart transplant recipient. Intern Med J 42(11):1268–1269

Ly C et al (2018) Psychedelics promote structural and functional neural plasticity. Cell Rep 23(11):3170–3182

Maclean KA et al (2012) Factor analysis of the mystical experience questionnaire: a study of experiences occasioned by the hallucinogen psilocybin. J Sci Study Relig 51(4):721–737

Madsen MK et al (2019) Psychedelic effects of psilocybin correlate with serotonin 2A receptor occupancy and plasma psilocin levels. Neuropsychopharmacology 44(7):1328–1334

Malcolm B, Thomas K (2021) Serotonin toxicity of serotonergic psychedelics. Psychopharmacology (Berl). https://doi.org/10.1007/s00213-021-05876-x

Moreno FA et al (2006) Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. J Clin Psychiatry 67(11):1735–40

Muthukumaraswamy SD, Forsyth A, Lumley T (2021) Blinding and expectancy confounds in psychedelic randomized controlled trials. Expert Rev Clin Pharmacol 14(9):1133–1152

Myerhoff BG (1974) Peyote hunt; the sacred journey of the Huichol Indians. Symbol, myth, and ritual series. Cornell University Press, Ithaca, p 285

Nayak SM et al (2021) Classic psychedelic coadministration with lithium, but not lamotrigine, is associated with seizures: an analysis of online psychedelic experience reports. Pharmacopsychiatry 54(5):240–245

Nicholas CR et al (2018) High dose psilocybin is associated with positive subjective effects in healthy volunteers. J Psychopharmacol 32(7):770–778

Nichols DE (2016) Psychedelics. Pharmacol Rev 68(2):264–355

Nichols DE, Grob CS (2018) Is LSD toxic? Forensic Sci Int 284:141–145

Olson DE (2021) The subjective effects of psychedelics may not be necessary for their enduring therapeutic effects. ACS Pharmacol Transl Sci 4(2):563–567

Osorio Fde L et al (2015) Antidepressant effects of a single dose of ayahuasca in patients with recurrent depression: a preliminary report. Braz J Psychiatry 37(1):13–20

Palhano-Fontes F et al (2019) Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. Psychol Med 49(4):655–663

Passie T (2018) The early uses of MDMA ('Ecstasy') in psychotherapy (1977–1985). Drug Science, Policy, and Law 4:1–19

Passie T, Seifert J, Schneider U, Emrich HM (2002) The pharmacology of psilocybin. Addict Biol. 7(4):357–64

Pokorny T et al (2016) Modulatory effect of the 5-HT1A agonist buspirone and the mixed non-hallucinogenic 5-HT1A/2A agonist ergotamine on psilocybin-induced psychedelic experience. Eur Neuropsychopharmacol 26(4):756–766

Preller KH et al (2017) The fabric of meaning and subjective effects in LSD-induced states depend on serotonin 2A receptor activation. Curr Biol 27(3):451–457

Raval MV et al (2008) Percutaneous transluminal angioplasty in the treatment of extensive LSD-induced lower extremity vasospasm refractory to pharmacologic therapy. J Vasc Interv Radiol 19(8):1227–1230

Roseman L, Nutt DJ, Carhart-Harris RL (2017) Quality of acute psychedelic experience predicts therapeutic efficacy of psilocybin for treatment-resistant depression. Front Pharmacol 8:974

Roseman L et al (2018) Increased amygdala responses to emotional faces after psilocybin for treatment-resistant depression. Neuropharmacology 142:263–269

Ross S (2018) Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress. Int Rev Psychiatry 30(4):317–330

Ross S et al (2016) Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. J Psychopharmacol 30(12):1165–1180

Sanches RF et al (2016) Antidepressant Effects of a Single Dose of Ayahuasca in Patients With Recurrent Depression: A SPECT Study. J Clin Psychopharmacol 36(1):77–81

Schindler EA, Sewell RA, Gottschalk CH, Luddy C, Flynn LT, Lindsey H, Pittman BP, Cozzi NV, D'Souza DC (2021) Exploratory controlled study of the migraine-suppressing effects of psilocybin. Neurotherapeutics. 18(1):534–43

Schultes RE, Hofmann A, Rätsch C (2001) Plants of the gods: their sacred, healing, and hallucinogenic powers. Rev. and expanded ed. Healing Arts Press, Rochester, p 208

Strassman RJ (1984) Adverse reactions to psychedelic drugs. A review of the literature. J Nerv Ment Dis 172(10):577–95

Strassman RJ (1996) Human psychopharmacology of N, N-dimethyltryptamine. Behav Brain Res 73(1–2):121–124

Strassman RJ et al (1994) Dose-response study of N, N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. Arch Gen Psychiatry 51(2):98–108

Studerus E, Gamma A, Vollenweider FX (2010) Psychometric evaluation of the altered states of consciousness rating scale (OAV). PLoS One 5(8):e12412

Studerus E et al (2011) Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. J Psychopharmacol 25(11):1434–1452

Studerus E et al (2012) Prediction of psilocybin response in healthy volunteers. PLoS One 7(2):e30800

Timmermann C, Watts R, Dupuis D (2020) Towards psychedelic apprenticeship: Developing a gentle touch for the mediation and validation of psychedelic-induced insights and revelations. Transcult Psychiatry. https://doi.org/10.31234/osf.io/j5768

Vaidya VA et al (1997) 5-HT2A receptor-mediated regulation of brain-derived neurotrophic factor mRNA in the hippocampus and the neocortex. J Neurosci 17(8):2785–2795

Vollenweider FX et al (1998) Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. NeuroReport 9(17):3897–3902

Watts R, Day C, Krzanowski J, Nutt D, Carhart-Harris R (2017) Patients' accounts of increased "connectedness" and "acceptance" after psilocybin for treatment-resistant deprerssion. J Human Psychol 57(5):520–564

Yaden DB, Griffiths RR (2021) The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. ACS Pharmacol Transl Sci 4(2):568–572

Yaden DB, Yaden ME, Griffiths RR (2021) Psychedelics in psychiatry-keeping the renaissance from going off the rails. JAMA Psychiat 78(5):469–470

Zeifman RJ et al (2021) Rapid and sustained decreases in suicidality following a single dose of ayahuasca among individuals with recurrent major depressive disorder: results from an open-label trial. Psychopharmacology 238(2):453–459