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Psychedelic drugs for psychiatric disorders

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ABSTRACT

Existing pharmacological treatments for psychiatric disorders have demonstrated limited efficacy, delayed onset of action, and significant burden of side effects. Recent findings from human studies with psychedelics have shown promise, demonstrating rapid and sustained clinical benefits of these compounds for a variety of psychiatric disorders. Classical psychedelics have a rich history and some of these compounds have been used in shamanic and spiritual ceremonies for millennia. The psychoactive effects of these drugs, particularly on human consciousness, have generated great scientific curiosity, and early research on psychedelics suggested their clinical benefits for psychiatric conditions, including alcohol use disorders and anxiety and depressive symptoms in terminal illness and life-threatening conditions. Since the 1990s, after a period of dormancy that followed the criminalization of psychedelic drugs since the Controlled Substance Act of 1970, the continued interest in their unique psychoactive effects along with the pursuit for novel and more effective treatments in psychiatry have led to a renewed interest in research on these compounds. While preliminary findings on psychedelics are encouraging, current evidence is still insufficient to support extensive use of these drugs routinely. Long-term safety and efficacy of these compounds remain unclear, and several clinical trials are underway and may add clarity to these questions. Therefore, this article intends to provide an overview of the evidence to date on psychedelic drugs – particularly psilocybin, MDMA, and LSD – for the treatment of psychiatric disorders.

1. Introduction

"What more can a person gain in life than what God-Nature itself reveals to him?" (Goethe)

As the pursuit for novel and more effective treatments in psychiatric disorders continues, findings from human research on psychedelic drugs have been encouraging. Psychedelics are a large group of natural, synthetic, and semisynthetic compounds with distinct pharmacological effects [1–3]. *(*Table 1.*)* The term "psychedelic," first coined by the British psychiatrist Humphrey Osmond in 1957, has been used to denote the "mind revealing" or "mind manifesting" properties associated with the use of such drugs like mescaline and psilocybin.

Psychedelic drugs differ from other psychoactive substances mainly by their effects on conscious experience that may include an altered sense of time and space, distorted perceptions of the environment, and dissociative symptoms. A renewed sense of purpose and the loss of normal boundaries of the self, often described as "ego dissolution," are also distinctive effects of these compounds [4]. To date, the biological mechanisms underlying these complex psychoactive effects remain poorly understood. The basic pharmacology of psychedelics includes agonist activity at serotonin (5HT) receptors, predominantly 5HT-2Ar, dopamine (D2) receptors, kappa opioid receptors, *N*-methyl-D-aspartate (NMDA)-receptor modulation, and monoamine transporters (serotonergic, dopaminergic, and noradrenergic) [1,2]. *(*Table 1.*)*

Evidence suggests that classical psychedelics, such as mescaline, ayahuasca, and psilocybin have been used in religious, shamanic, and spiritual ceremonies for millennia by South and Mesoamerican, Asian, and European cultures particularly seeking the "*entheogenic* – "*generating God within*" – properties of these drugs [5–7]. Some of these compounds, such as mescaline, continue to be used in religious ceremonies by the Native American Church in the U.S. and Canada to this day, similarly to ayahuasca and dimethyltryptamine (DMT) by indigens in Amazonia and

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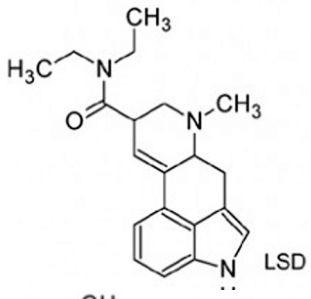
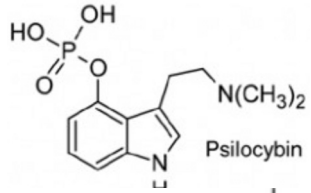
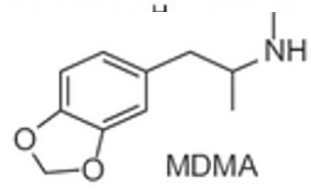
other regions of South America (Santo Daime Church). Interestingly, the use of psychedelics for religious practices under specific circumstances has been recognized and even protected by law in countries such as the US (American Indian Religious Freedom Act of 1978) [8–10].

Given their complex and unique psychoactive effects, psychedelic drugs have raised great scientific curiosity, with a large number of clinical studies conducted in the US in the 1950s and 1960s [11,12]. Interestingly, LSD and psilocybin became more extensively used to facilitate progress in psychotherapy through self-reflection, ego dissolution, and access to unconscious material. These compounds were eventually marketed under brand names (Delysid® and Indocybin®, respectively) by Sandoz during the 1950s and 1960s [13,14]. Curiously, psychedelics were even used as "truth serums" for intelligence and military purposes around this point in history [13,15,16].

Early studies on psychedelics suggested safety of these compounds even in medically complex patients, although lack of rigorous scientific methodology and reports of adverse events limit the reliability of early findings on the safety of these compounds. Moreover, some psychedelic compounds, such as mescaline and LSD, were believed to provoke exceptional insights into the essence of the creative process, which resulted in great curiosity and interest outside the medical field. Widespread use of psychedelics for non-medical purposes and careless experimentation with these drugs led to negative outcomes [17–21]. Furthermore, their association with political activism and the counterculture movement of the 1960s resulted in significant stigma against these drugs [21,22], which culminated with their criminalization as Schedule I drugs by the Controlled Substance Act of 1970 [23].

Unsurprisingly, the new scheduling and classification of psychedelic drugs hindered research with these compounds, resulting in a period of dormancy of human research with psychedelics [24]. However, continued interest in their unique psychoactive effects along with increased need for novel and more effective pharmacotherapies for psychiatric disorders have led to a renewed interest in the therapeutic potential of psychedelics [25,26]. Since the 1990s, there has been a resurgence in psychedelic research, with multiple studies assessing the potential efficacy of psychedelics as novel treatments for a broad range of psychiatric disorders, including treatment-resistant depression (TRD), posttraumatic stress disorder (PTSD), anxiety, adjustment disorders in terminal illness and life-threatening conditions, and substance use disorders. *(*Table 2*.)* Emerging evidence of efficacy of psilocybin and MDMA have granted these compounds FDA designation as "breakthrough therapies" for TRD and PTSD, respectively, and phase II and III trials are under way [27–33]. These promising results may represent a paradigm shift in the field of psychiatry, introducing the field into a new era of interventional psychiatry with these novel therapeutics, instilling hope into individuals in dire need. Therefore, this article intends to provide an overview of the clinical applications of psychedelic drugs and psychedelic-assisted therapy for psychiatric conditions. The goal is to highlight the evidence to date from clinical research on psilocybin, MDMA, and LSD, since these drugs have been more extensively studied,

Table 1
Basic pharmacology and classification of psychedelic drugs.

Type and Class	Molecular structure	Dose, route, physiological effects	Mechanism of action and special comments
LSD Ergolines Semisynthetic (*Claviceps purpurea*)		dose: 40-200μg oral/IV use onset of effects typically within 30–60 min, peak within 2-4 h, and last between 5 and 10 h	Semisynthetic, derived from the class of ergolines (*Claviceps purpurea*). Mechanism of action - primarily mediated by the serotonergic agonism (5HT-1A and 5HT-2A) in the dorsal raphe and effects on dopaminergic, Trace Amine Associate receptor 1 ($TAAR_1$) and 5HT-2A systems in the ventral tegmental area. LSD has high potency and high affinity for 5HT-2A receptors. First synthesized by the Swiss scientist Albert Hofmann in 1938, LSD was marketed under the brand name of Delysid® (LSD 25) until 1965, when Sandoz removed it from the market due to extensive non-medical use and experimentation with this drug.
Psilocybin** Indole ethylamines natural – plant-based		dose: 10-40 mg; 1-5 g or dried mushrooms oral use onset of effects typically within 30–60 min, peak within 90–180 min, and last ~6 h	Naturally occurring alkaloid from the class of indole ethylamine present in over 200 different species of fungus, the latter also known as "magic mushrooms." Psilocybin has been used as entheogenic** substance in religious and sacramental ceremonies by South and Central American natives for centuries. Curiously, the Swiss scientist Albert Hofmann, who synthesized LSD in 1938, also isolated psilocybin. Similarly to LSD, psilocybin was also marketed by Sandoz under brand name Indocybin®.
MDMA* 3,4-methylenedioxy-methylamphetamine (MDMA), also known as "ecstasy" Phenylethylamines synthetic*		dose: 80-150 mg tablets oral use onset of effects typically within 30 min, peak within 1.5–2 h, and last ~10 h	Synthetic, from the class of phenylethylamines. MDMA shares molecular similarities with stimulants and psychedelics. Synthesized by Merk & CO. in 1912, the psychoactive effects of MDMA were only reported in the 1970s. Pharmacologically, MDMA induces monoamine release, serotonin, and norepinephrine transporter inhibition, agonism of 5HT-1A, 2A, and 2C receptors. Interestingly, it has been suggested that MDMA releases oxytocin, which is believed to mediate, at least in part, prosocial and empathogen properties of this compound.

LSD – lysergic acid diethylamide; MDMA – 3,4-methylenedioxy-methylamphetamine.
*Empathogens or entactogens ("en" – Greek – "within," "tactus" Latin "touch," "gen" – Greek "generate") – are believed to have the potential to enhance closeness and connectedness, ability to decrease anxiety, increase trust and self-acceptance. ** Entheogen – God within (En – within, Greek Theos – God, gen – produce) – used in spiritual or religious rituals.

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Table 2
Examples of Clinical Trials on MDMA, psilocybin, and LSD.

Author	Design	N	Target Symptoms	Intervention	Outcome
MDMA					
Mithoefer et al. 2011 [34]	Randomized double-blind crossover	n=23	PTSD	MDMA 125 mg plus optional 62.5 mgvs Placebo (lactose)	Significant reduction in PTSD symptom severity. The mean change in CAPS scores 2 months after the second experimental session was −53.7 for the MDMA group and − 20.5 for placebo group.
Mithoefer et al. 2018 [35]	Randomized, double-blind, dose-response, phase 2 trial	$n = 26$	PTSD	30 mg ($n = 7$), 75 mg (n = 7), or 125 mg ($n = 12$) of MDMA plus psychotherapy	75 mg and 125 mg groups had significantly greater decreases in PTSD symptom severity (mean change CAPS-IV total scores of −58·3 [SD 9·8] and − 44·3 [28·7]; $p = 0·001$) than the 30 mg group (−11·4 [12·7]).
Mitchell et al. 2021 [43]	randomized, double-blind, placebo-controlled, multi-site phase 3 clinical trial	$n = 90$	PTSD	MDMA (80 to 120 mg, $n = 46$) vs. placebo ($n = 44$)	MDMA was found to induce significant and robust attenuation in CAPS-5 score compared with placebo ($P < 0.0001$, d = 0.91) and to significantly decrease the SDS total score ($P = 0.0116$, d = 0.43). The mean change in CAPS-5 scores in participants completing treatment was −24.4 (s.d. 11.6) in the MDMA group and − 13.9 (s.d. 11.5) in the placebo group.
Ot'alora et al. 2018 [36]	randomized phase 2 controlled trial	n = 28	PTSD	active doses (100 and 125 mg) with a low dose (40 mg) of MDMA administered during eight-hour psychotherapy sessions.	active groups had the largest reduction in CAPS scores at the primary endpoint, with mean (standard deviation) changes of −26.3 (29.5) for 125 mg, −24.4 (24.2) for 100 mg, and − 11.5 (21.2) for 40 mg. PTSD symptoms remained lower than baseline at 12-month follow-up ($p < 0.001$) with 76% ($n = 25$) not meeting PTSD criteria.
Wolfson et al. 2020 [39]	Randomized, double-blind, placebo-controlled study	$n = 18$	anxiety and other psychological distress related to life-threatening illnesses	MDMA (125 mg, $n = 13$) or placebo ($n = 5$)	MDMA group had a greater mean (SD) reduction in STAI-Trait scores, − 23.5 (13.2), indicating less anxiety, compared to placebo group, − 8.8 (14.7); results did not reach a significant group difference ($p = 0.056$). Hedges' g between-group effect size was 1.03 (95% CI: - 5.25, 7.31).
Jerome et al. 2020 [40]	longitudinal pooled analysis of six phase 2 trials	==105	PTSD	two to three active doses of MDMA (75–125 mg) during blinded or open-label psychotherapy sessions with additional non-drug therapy sessions.	significant reduction in CAPS-IV total severity scores from baseline to treatment exit (LS mean (SE) = − 44.8 (2.82), $p < 0.0001$), with a Cohen's d effect size of 1.58 (95% CI = 1.24, 1.91). CAPS-IV scores continued to decrease from treatment exit to LTFU (LS mean (SE) = − 5.2 (2.29), $p < 0.05$), with a Cohen's d effect size of 0.23 (95% CI = 0.04, 0.43). The number of participants who no longer met PTSD criteria increased from treatment exit (56.0%) to LTFU (67.0%).
Danforth et al. 2018 [42]	Randomized, double-blind, placebo-controlled study	N = 12	Social anxiety in ASD	MDMA (75 to 125 mg, n = 8) or inactive placebo (0 mg, n = 4) during two 8-h psychotherapy sessions (experimental sessions) in a controlled clinical setting	rapid and durable improvement in social anxiety symptoms in autistic adults following MDMA-assisted psychotherapy.
Psilocybin					
Moreno et al. 2006 [82]	modified double-blind trial	n = 9	Obsessive-compulsive disorder	up to 4 single-dose exposures to psilocybin in doses ranging from sub-hallucinogenic (25 microg/kg) to (100 microg/kg), medium (200 microg/kg), and high (300 microg/kg) doses. 8-h sessions. The Yale-Brown Obsessive Compulsive Scale (YBOCS) and a visual analog scale measuring overall OCD symptom severity administered at 0, 4, 8, and 24 h post-ingestion.	Marked decreases in OCD symptoms of variable degrees were observed in all subjects during 1 or more of the testing sessions (23%–100% decrease in YBOCS score).
Roseman et al. 2018 [88]	open-label	$n = 20$	Treatment-resistant depression	two separate dosing sessions with psilocybin. Psychological support. fMRI scans one week prior to the first session and one day after the second and last sessions.	rapid and enduring improvements in depressive symptoms post psilocybin. Increased responses to fearful and happy faces in the right amygdala post-treatment, and right amygdala increases to fearful versus neutral faces were predictive of clinical improvements at 1-week.
Carhart-Harris et al. 2016 [85]	Open-label	n=12	moderate-to-severe, unipolar, treatment-resistant major depression	Psilocybin 10 mg, and 25 mg 2 weeks later. No comparison group	Relative to baseline, depressive symptoms were markedly reduced 1 week (mean QIDS difference − 11·8, 95% CI -9·15 to −14·35, p = 0·002, Hedges' g = 3·1) and 3 months (−9·2, 95% CI -5·69 to −12·71, p = 0·003,

(*continued on next page*)

Table 2 (*continued*)

Author	Design	N	Target Symptoms	Intervention	Outcome
					Hedges' g = 2) after high-dose treatment. Marked and sustained improvements in anxiety and anhedonia were also noted.
Carhart-Harris et al. 2021 [93]	Phase 2, Randomized double-blind controlled trial	*n* = 59	Long-standing, moderate-to-severe major depressive disorder	Psilocybin 25 mg 2 doses 3 weeks apart plus placebo during 6-week or Psilocybin 1 mg 2 doses 3 weeks apart plus escitalopram 10 mg.	QIDS-SR-16 scores at week 6 did not show a significant difference between psilocybin and escitalopram. Secondary outcomes generally favored psilocybin over escitalopram, but the analyses were not corrected for multiple comparisons.
Griffiths et al. 2016 [78]	Randomized double-blind crossover	*n* = 51	depression and anxiety in patients with life-threatening cancer	Psilocybin 22 or 30 mg 70 kg vs Psilocybin, 1 or 3 mg/70 kg	At 6-month follow-up, these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety.
Ross et al. 2016 [80]	Randomized, double-blind, placebo-controlled, crossover trial	*n* = 29	Cancer-related anxiety and depression	Psilocybin 0.3 mg/kg vs Niacin	At 6.5-month follow-up, psilocybin was associated with enduring anxiolytic and anti-depressant effects (~ 60–80% of participants continued with clinically significant reductions in depression or anxiety), sustained benefits in existential distress and quality of life, as well as improved attitudes towards death.
Johnson et al. 2014 [83]	Open-label	n = 15	Tobacco use disorder	Psilocybin 20 mg/70 mg or 30 mg/70 kg. No comparison group	Biomarkers assessing smoking status, and self-report measures of smoking behavior demonstrated that 80% of participants showed 7-day point prevalence abstinence at 6-month follow-up, which substantially exceeds rates commonly reported for other interventions (typically <35%).
Johnson et al. 2017 [76]	Long-term follow-up study	n = 15	Tobacco use disorder	N/A	At 12-month follow-up, 10 participants (67%) were confirmed as smoking abstinent. At long-term follow-up, nine participants (60%) were confirmed as smoking abstinent.
Bogenshutz et al. 2015 [84]	Open-label	*n* = 10	Alcohol use disorder	Psilocybin 0.3 mg/kg, and 0.4 mg/kg 4 weeks later, Motivational Enhancement Therapy, preparatory sessions No comparison group	Abstinence did not increase significantly in the first 4 weeks of treatment (when participants had not yet received psilocybin), but increased significantly following psilocybin administration ($p < 0.05$). Gains were largely maintained at 36 weeks. The intensity of effects in the first psilocybin session (at week 4) strongly predicted change in drinking during weeks 5–8 ($r = 0.76$ to $r = 0.89$) and also predicted decreases in craving and increases in abstinence self-efficacy during week 5
LSD					
Gasser et al. 2014 [65]	double-blind, randomized, active placebo-controlled	n = 12	Anxiety associated with life-threatening disease	LSD-assisted psychotherapy sessions 2 to 3 weeks apart (LSD 200 μg) vs. Active placebo 20 μg	At the 2-month follow-up, positive trends were found via the State-Trait Anxiety Inventory (STAI) in reductions in trait anxiety ($p = 0.033$) with an effect size of 1.1, and state anxiety was significantly reduced ($p = 0.021$) with an effect size of 1.2. STAI reductions were sustained for 12 months.
Schmid et al. 2018 [69]	Randomized double-blind crossover	*n* = 16	Healthy subjects	LSD-assisted psychotherapy – 1 session (LSD 200 μg)	positive attitudes about life and/or self, positive mood changes, altruistic/positive social effects, positive behavioral changes, and well-being/life satisfaction on the PEQ (persisting effects questionnaire) and MS (mysticism scale)

besides a discussion on methodological challenges and future directions of human research on psychedelics.

This article is part of the Special issue "Psychedelic and Interventional Psychiatry" edited by Mark Gold. Noteworthy, a review of pre-clinical evidence is beyond the scope of this article. Moreover, ayahuasca, ibogaine, mescaline, and other hallucinogens will be covered elsewhere in this special edition.

2. MDMA - 3,4-methylenedioxy-methylamphetamine

Early studies with MDMA explored the safety and efficacy of this drug for alcohol use disorder, obsessive-compulsive disorder, adjustment reactions to end-of-life conditions, and trauma-reactions. However, similarly to other hallucinogens, research with MDMA was stalled after its criminalization in 1985, and the first randomized, placebo-controlled clinical trial assessing safety and efficacy of MDMA-assisted psychotherapy for treatment-resistant PTSD in modern psychedelic research in the US dates back 2010 [34]. In this pilot study, Mithoefer *et.al* found a significant reduction in Clinician-Administered PTSD Scale (CAPS) scores in the intervention group ($n = 12$), with rates of clinical response of 10/12 (83%) in the treatment group versus 2/8 (25%) in the placebo group ($n = 8$) [34]. No drug-related serious adverse events or clinically significant autonomic and cardiovascular side effects, particularly elevated blood pressure, were observed [34].

Since after this initial trial, multiple studies exploring the safety, neurobiology, and efficacy of MDMA-assisted psychotherapy have been conducted.

A randomized, double blind, dose response phase 2 clinical trial assessing efficacy and safety of MDMA-assisted psychotherapy for PTSD in military veterans, firefighters, and police officers randomly assigned to receive 30 mg ($n = 7$), 75 mg (n = 7), or 125 mg ($n = 12$) of MDMA plus psychotherapy found greater reduction in PTSD symptom severity (mean change CAPS-IV total scores of −58·3 [SD 9·8] and − 44·3 [28·7]; $p = 0{\cdot}001$) in the 75 mg and 125 mg intervention groups compared to the 30 mg group (−11·4 [12·7]). Moreover, PTSD symptoms were significantly reduced at the 12-month follow-up compared with baseline after all groups had full-dose MDMA. Several adverse events were reported by 20 participants in this study. Of these adverse events, four (5%) were serious, and three were deemed unrelated to study drug treatment [35]. Similar results were demonstrated in a phase 2, double-blind, randomized clinical trial, dose response comparison (100–125 mg vs. 40 mg) of MDMA administered during eight-hour psychotherapy sessions for PTSD ($N = 28$). In this study, significant improvements in PTSD symptoms were reported in the active-dose groups (125 and 100 mg, respectively) compared with low-dose (40 mg) group at 1 month and 12-month follow-up. No drug-related serious events were observed or reported in this study [36].

A double blind, placebo-controlled study examining the effects of MDMA on emotional memory found that MDMA seems to attenuate the encoding and retrieval of salient details from emotional events, which seems to be of particular clinical utility in trauma-related reactions and conditions such as PTSD [37]. Similarly, a randomized clinical trial of MDMA-assisted psychotherapy for PTSD found that heightened openness and decreased neuroticism may be part of the underlying mechanisms of action of this intervention, and more sustained improvements in PTSD symptoms may occur in response to personality changes that may be long-lasting [38]. MDMA-assisted psychotherapy has also been tested for the treatment of anxiety and psychological distress related to life-threatening conditions (125 mg, $N = 13$). In this study, the MDMA group had a greater mean reduction in the State-Trait Anxiety Inventory Trait scores compared with the placebo group ($N = 5$), indicating less anxiety, although results did not achieve statistical significance ($p = 0.056$) [39].

A longitudinal pooled analysis of six phase 2 trials of MDMA (75–125 mg) during blinded or open-label psychotherapy sessions with additional non-drug therapy sessions showed a significant reduction in PTSD symptoms 1 to 2 months after MDMA-assisted psychotherapy, and symptom improvement continued at least 12 months post-treatment. Interestingly, in this analysis, the number of participants who no longer met PTSD criteria increased from treatment exit (56.0%) to 12-month follow-up (67.0%) [40]. Interestingly, MDMA-assisted psychotherapy has been posited as a new treatment model for social anxiety in adults with autism spectrum disorder [41]. A recent randomized, double-blind, placebo controlled pilot study demonstrated rapid and sustained improvements in social anxiety symptoms following MDMA-experimental session (75 to 125 mg, $n = 8$) for adults with autism and marked to severe social anxiety. In this study, social anxiety symptoms remained the same or continued to improve for most participants in the MDMA group even after completing the active treatment phase, and clinical benefits were still present at 6-month follow-up [42]. Lastly, a phase III randomized, multicenter, placebo-controlled study testing the efficacy and safety of MDMA-assisted therapy for the treatment of severe PTSD found that MDMA significantly attenuated PTSD symptomatology, with 28 of the 42 participants (67%) in the MDMA group no longer meeting criteria for PTSD at the primary study endpoint (18 weeks after intervention) [43].

To date, serious adverse events involving the administration of MDMA in clinical trials have been rare and non-life threatening. Most common side effects include poor appetite and autonomic reactions, including increase in heart rate, blood pressure, and body temperature. However, neurotoxicity and damage to serotonergic terminals associated with MDMA exposure remain a matter of debate [44–46]. While some argue that these have been portrayed as exaggerated risks to discourage research on these compounds, others claim that results are mostly from an animal models, particularly rodents and primates, and the extrapolation of these findings to human subjects would not be accurate. Additionally, emerging evidence from human studies has somewhat challenged some of these early findings [47,48]; however, further research is warranted to better clarify more nuanced risks associated with these compounds in humans. It is important to note that, given data on efficacy and safety of MDMA-assisted therapy from phase 2 and 3 trials, in 2017, the FDA granted "breakthrough therapy" designation to MDMA-assisted therapy for PTSD, which allows expedited drug development and priority review to drug candidates that may offer substantial advantages over existing therapeutics for patients with serious or life-threatening conditions. Thus, given that preliminary findings from MDMA-assisted psychotherapy hold promise, if phase 3 trials are able to consistently replicate efficacy and safety data in large-scale studies, MDMA-assisted psychotherapy for PTSD may eventually receive FDA-approval for the treatment of PTSD.

3. Lysergic acid diethylamide (LSD)

LSD and other psychedelicdrugs prompted considerable interest in psychiatric research since the 1950s, leading to >1000 scientific publications by the 1970s [4,49]. Early research on LSD focused on the safety of this compound, besides its clinical utility for depression and anxiety in terminal illness, alcohol use disorder, "obsessional depression and neurosis," personality disorders, and depression [50–54]. Given psychotomimetic properties and dissociative symptoms, LSD was also posited as a disease model of schizophrenia and other psychotic disorders [55,56]. More robust findings from early research on LSD came from studies on its efficacy for alcohol use disorder [57–61], and a recent meta-analysis of 6 randomized clinical trials conducted between 1960s and 1970s showed large and significant effects of a single dose LSD efficacy on reducing problematic drinking and number of drinking days compared to control conditions ($n = 536$) [62]. Modern research with LSD has been scarce compared to studies with psilocybin and MDMA. Studies exploring the mechanisms of action of LSD and effects on conscious experiences, prosocial behaviors, creativity, and mystical experiences, neural substrates of emotional processing, and the effects of LSD on anxiety and depression in life-threatening conditions have been conducted, and even the use of LSD for chronic pain and cluster headaches has been recently explored [63–69]. Moreover, proponents of LSD microdosing, the practice of consuming small, sub-hallucinogenic doses of LSD, argue that this practice may provide significant benefits for mood, anxiety, and enhanced cognition [70,71]. Interestingly, a recent naturalistic study has shown that moderate or high dose LSD or psilocybin use was associated with persisting reductions in cannabis, opioid, or stimulant use in individuals who met criteria for severe substance use disorders at baseline, raising questions on the potential benefits of these drugs as harm reduction strategies in the field of addiction [72].

4. Psilocybin

Early experiments and contemporary studies have demonstrated efficacy and safety of psilocybin for a variety of conditions, including anxiety and depressive symptoms in life-threatening conditions, TRD, obsessive-compulsive disorder (OCD), and substance use disorders [73–76].

A double-blind, placebo-controlled pilot study ($n = 12$) of psilocybin (0.2 mg/kg) treatment for anxiety in patients with advanced-stage cancer demonstrated a significant reduction in anxiety at 1 and 3 months after treatment and no clinically significant adverse events with psilocybin [77]. Similarly, data from a randomized, double-blind, cross-over trial ($n = 51$) comparing the effects of a very low (placebo-

like) dose (1–3 mg/70 kg) vs. high dose (22 to 30 mg/70 kg) psilocybin demonstrated substantial and sustained decrease in depression and anxiety following a single-dose psilocybin in patients with life-threatening cancer [78]. In this study, the effects of psilocybin on depression and anxiety were still detected in the intervention group even at 5-weeks and 6-months follow-up. Enhanced quality of life, life meaning and optimism, and reduction in death anxiety were also reported by participants, with near to 80% of participants endorsing sustained improvements at 6-month follow up [114]. In a similar study, single-dose psilocybin produced substantially greater effects including perceptual changes, mystical-type experiences, and labile mood acutely, and reduction in anxiety and depressive symptoms at 5-week, also demonstrating long-lasting clinical benefits [79]. Moreover, a randomized, crossover clinical trial found rapid and sustained anxiety and depression symptom reduction following psilocybin treatment (0.3 mg/kg), along with decreases in cancer-related demoralization and hopelessness, improved spiritual wellbeing, and increased quality of life [80]. In this study, sustained benefits in existential distress and quality of life, as well as improved attitudes towards death seemed to be mediated by the intensity of the mystical experience triggered by psilocybin, which seems to be consistent with several reports in the literature as a predictor of psychedelic response [81].

Psilocybin was safe, well-tolerated, and associated with marked decrease in core symptoms of OCD in a randomized, double-blind clinical trial [82]. Since this seminal study in 2006, two ongoing phase 2 randomized clinical trials are assessing the effects of psilocybin on OCD symptoms. Furthermore, preliminary evidence suggests efficacy of psilocybin for substance use disorders, including alcohol use disorder and nicotine and tobacco use disorder. For instance, a recent open-label study ($N = 15$) found that two to three moderate-to-high dose (20 and 30 mg/70 kg) psilocybin in combination with cognitive behavioral therapy (CBT) resulted in substantially higher 6-month smoking abstinence rates compared to standard of care (other medications for smoking cessation or CBT alone). At 12-month follow-up, 10 participants (67%) were confirmed as smoking abstinent, and 13 participants (86.7%) rated their psilocybin experiences among the five most personally meaningful and spiritually significant experiences of their lives [83]. Moreover, in a proof-of-concept study of psilocybin for alcohol use disorder, abstinence rates increased significantly following psilocybin administration, and therapeutic gains were largely maintained at follow-up to 36 weeks [84]. Additionally, as previously noted, in a naturalistic study, moderate or high doses of LSD or psilocybin mushrooms were associated with persisting reductions in cannabis, opioid, or stimulant use in individuals with severe substance use disorders at baseline [72]. New studies assessing the efficacy of psilocybin for the treatment of other substance use disorders, such as cocaine and opioid use disorders, are underway. If successful, psilocybin may introduce the field of Addiction into a new era of treating substance use disorders with psychedelic drugs.

Yet, more compelling evidence on the efficacy of psilocybin comes from studies on psilocybin for TRD. Findings from an open-label feasibility trial on the effects of a single-dose psilocybin intervention for TRD demonstrated significant and sustained improvements of depressive symptoms at one week and three months post-intervention [85], and brain imaging studies assessing neural correlates of psilocybin for TRD have demonstrated changes in brain areas highly involved in emotional regulation and processing, such as amygdala and prefrontal cortex [86–88]. Interestingly, evidence suggests that not only emotions but also brain function were altered up to 1 month after a single high dose psilocybin [89]. A Randomized clinical trial on the effects of psilocybin-assisted therapy on major depressive disorder (MDD) suggests that psilocybin in combination with psychotherapy is efficacious in treating MDD [90]. Given robust and compelling evidence of rapid and sustained benefits of psilocybin, particularly for TRD and MDD, the FDA has twice granted psilocybin a breakthrough therapy designation since 2018. Phase 2 and 3 trials are underway.

Studies with psilocybin showed that greater mystical experiences were a strong predictor of positive long-term effects on mood and personality in healthy subjects [91] and efficacy and duration of clinical benefits in individuals with depression, anxiety, and substance use disorder [91,92]. Noteworthy, the comparison between psychedelics and standard of care is still lacking, and a recent phase 2, double-blind, randomized, controlled trial comparing psilocybin with escitalopram in patients with moderate-to-severe major depressive disorder failed to demonstrate significant differences in antidepressant effects between the two groups [93]. Larger and longer trials are needed to compare psilocybin with established FDA-approved treatments for depression.

5. Discussion

Once a major issue, the widespread non-medical use of psychedelics has significantly decreased since the Controlled Substance Act (CSA) of 1970. For instance, according to the 2018 National Survey on Drug Use and Health (NSDUH), the lifetime prevalence of hallucinogen use in the U.S. population aged 12 and older is 15.8%, with estimates of 2% of the U.S. population reporting past-year use, and 0.6%, past-month use, which is considered relatively low when compared to other drugs of abuse [94].

Although preliminary at large, modern research on psychedelics seems to hold promise, with greater clinical benefits demonstrated for MDD, TRD, PTSD, OCD, anxiety and depression in terminal illness and life-threatening conditions, and substance use disorders. (Table 2.) Pilot studies and small trials have demonstrated overall safety and efficacy of these drugs, and Phase 2 and 3 trials are underway, particularly since MDMA- and psilocybin-assisted therapy have received breakthrough therapy designation by the FDA in recent years [27–33].

Nonetheless, the development of novel therapeutics remains a daunting challenge, and research on psychedelics has proven to be no exception [17,95]. For instance, overly strict regulations have hindered research on psychedelics and access to pure compounds; on the other hand, more flexible regulations and broad use of these drugs in medical settings may also create new challenges since it may change the public's perception of harm and lead to a new surge of psychedelic use for non-medical reasons, reminiscent of the events in the 1950s and 60s. Moreover, LSD- and psilocybin-microdosing, the practice of consuming small sub-hallucinogenic doses of these compounds, seems to have increased over the past years, with proponents of this practice and anecdotal reports suggesting its benefits for creativity, mood-altering effects, cognitive enhancement, self-discovery, and renewed sense of purpose and meaning [70,96,97]. Recent data, however, suggest no significant differences in emotional state, mood, energy, creativity, and anxiety in a naturalistic study exploring the effects of psychedelic microdosing compared with placebo, suggesting that the anecdotal effects of psychedelic microdosing may be explained by the placebo effect [98].

Methodological limitations not only from early research on psychedelics, but also modern studies with these compounds remain a matter of concern. Small sample sizes, open-label study designs, challenges in masking interventions, potential selection biases, and participants' expectancy favoring psychedelic drugs continue to represent major limitations of modern research with psychedelics. For instance, a recent systematic review exploring clinical and biological predictors of response to psychedelics found that the intensity of acute psychedelic experience was the main predictive factor of response for alcohol and tobacco use disorders, treatment-resistant depression, and anxiety and depression in life-threatening conditions, but not in obsessive-compulsive disorder [81]. These findings may exemplify some of the challenges in psychedelic research, including masking interventions due to unique psychoactive effects of psychedelics. For the same reason, the use of placebos remains a challenge, and evidence suggests that research participants and investigators can often predict treatment allocation accurately, even when controlled for active placebos [99–102].

Highly structured study settings and intensive psychosocial and behavioral interventions may also favor psychedelic interventions, especially in non-controlled studies. For instance, while standard of care – e.g., antidepressant treatment – typically encompasses psychoeducation and a discussion of risk-benefit for informed consent and decision-making, it is a limited clinician-patient interaction unparalleled to protocols on MDMA, for example, where an individual may receive three 90-min preparatory sessions; two 8-h MDMA sessions 1 month apart; a 90-min integrative session the morning after; daily 15–60-min phone calls occurring for 7 days following each experimental session; and finally, two non-drug integrative sessions after each blinded session approximately weekly. For this very same reason, it seems unlikely that psychedelic-assisted therapies will become first-line interventions in psychiatry, given potential costs and other needs, such as appropriate settings and trained personnel. Conversely, advantages of psychedelics that may include single-dose interventions over daily dosing medications may result in increased efficacy and overall treatment compliance with these drugs.

Particularly remarkable have been the results of psychedelic-assisted therapy for alcohol use disorder and smoking cessation, which, if confirmed in large scale studies, may represent a new era of treating substance use disorders with psychedelics [73]. Yet, trials comparing psychedelic drugs and standard of care are still largely lacking. For instance, a recent phase 2, double-blind, randomized trial comparing psilocybin and escitalopram for depression did not show a significant difference in antidepressant effects between psilocybin and escitalopram for moderate-to-severe depression at week 6 [93]. While one may argue that these results show promise and could potentially represent non-inferiority of psilocybin compared with established treatments for depression, it is well-known that antidepressants usually take 4–6 weeks to be effective [103,104], and brief duration of treatment may have unfavored escitalopram intervention in this study protocol, for instance.

Lastly, although overall well-tolerated, potential risks of psychedelic drugs should not be neglected, as it may include psychological distress, persistent perceptual disturbances, acute suicidality, autonomic and cardiovascular, neurocognitive, besides drug-drug interactions [105–107]. Potential for abuse remains a matter for debate, although addiction liability seems low given low reinforcing effects of these drugs [17]. Moreover, the effects on brain development remain largely unknown, which can be particularly concerning when enrolling healthy volunteers under the age of 25 in research protocols. Long-term effects of these drugs are yet to be determined, although anecdotal and naturalistic findings suggest safety and tolerability of these compounds. It is important to note that mechanisms of action of some psychedelics include reversible inhibition of monoamine oxidase enzymes, which, in combination with antidepressants and other psychotropic drugs, may lead to serious and potentially life-threatening conditions, such as serotonin toxicity [108–110]. Moreover, it also raises questions on the safety and other potential negative consequences if psychotropic medication discontinuation is needed or desired prior to psychedelic interventions.

6. Conclusion

Human research on psychedelics is now at a crossroads with significant promise and many challenges. The social and scientific value of these compounds seem compelling as they emerge as potential treatments for a broad range of psychiatric disorders. Taken together, preliminary findings on psychedelics instill hope even to individuals suffering from pervasive, severe, and difficult-to-treat psychiatric conditions. However, at this point, the use of psychedelics for medical reasons remains experimental, and current data are still insufficient to support the use of psychedelics, including “microdosing” strategies, routinely. Methodologically robust, larger, and longer trials are needed to compare psychedelic drugs with established treatments and standard of care, and evidence to date should be used to support further research in this area.

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Declaration of Competing Interest

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