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Medical Uses and Adverse Effects of Psilocybin

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Lessons Learned at the Interface of Medicine and Psychiatry

The Psychiatric Consultation Service at Massachusetts General Hospital sees medical and surgical inpatients with comorbid psychiatric symptoms and conditions. During their twice-weekly rounds, Dr Stern and other members of the Consultation Service discuss diagnosis and management of hospitalized patients with complex medical or surgical problems who also demonstrate psychiatric symptoms or conditions. These discussions have given rise to rounds repors that will prove useful for clinicians practicing at the interface of medicine and psychiatry.

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Would you be surprised to learn that some of your patients are interested in psilocybin to address their medical conditions, ranging from depression to headaches, and may even be considering trying it on their own? Have you wondered whether you might recommend psilocybin to your patients with cancer? Have you been uncertain about the nature and severity of psilocybin's side effects? If you have, the following case vignette and discussion might prove useful.

CASE VIGNETTE

Mr D, a 65-year-old man with a history of diabetes, hyperlipidemia, and depression who has been struggling with depression for the past year despite several trials of selective serotonin reuptake inhibitors (SSRIs), including sertraline, fluoxetine, and now escitalopram, presented to your office inquiring about psilocybin after a family member told him about a documentary on psychedelics successfully being used for treatment-resistant psychiatric illness. He remembered being curious about psychedelics in his youth, back in the 70s, but he refrained from using them since they were associated with the counterculture, and he had never been one to use drugs. He wondered whether he might be a good candidate for psilocybin for depression. He did not have a history of mania or psychosis and did not currently use any illicit substances or alcohol.

DISCUSSION

What Are Psychedelics and How Do They Work?

The term *psychedelic* was first coined by the British psychiatrist Humphrey Osmond; it was derived from the Greek words *psyche* for mind and *delic* for manifest, and so psychedelics are sometimes referred to as mind-manifesting drugs. There are 3 major classes of psychedelics. There are the classic psychedelics, also sometimes referred to as entheogens because they have been used to produce nonordinary states of consciousness for religious/spiritual purposes. They are primarily agonists of the serotonin 5-HT_{2A} receptor and include lysergic acid diethylamide, psilocybin (originally derived from the mushrooms of the genus *Psilocybe*), mescaline (derived from peyote), N,N-dimethyltryptamine (DMT; a major ingredient of ayahuasca), and 5-methoxy-DMT (5-MeO-DMT) (derived from some plants and toad species).[1] The second class of psychedelics are the empathogens, to which 3,4-methylenedioxymethamphetamine (MDMA) belongs, so named because they induce feelings of empathy and relatedness. MDMA also acts on 5-HT_{2A} receptors, but it is much weaker than the classic psychedelics. In addition, it binds to several other receptors, including adrenergic receptors, as well as monoamine transporters, and it prevents reuptake. Finally, there are the dissociative agents, which are sometimes referred to as psychedelics; these drugs include ketamine, ibogaine, and Salve or Salvinorin A. Aside from ketamine and Salvinorin A (which is not a scheduled medication), all of these compounds are classified by the Drug Enforcement Administration as schedule I drugs, which means that, at the federal level,

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Clinical Points

- Psilocybin-assisted psychotherapy for depression and alcohol use disorder has the best evidence base to date; however, even those data are preliminary, as phase 3 trials are only beginning.
- Patients can only access psilocybin legally for therapeutic or medical purposes through clinical trials, if they qualify.
- Positive results with psilocybin-assisted therapy are from psilocybin that is administered in well-controlled studies with great attention to preparation, support, and the setting of administration, which is different from psilocybin's recreational use.
- Adverse effects of psilocybin-assisted psychotherapy are still being studied and far from being well characterized until larger phase 3 trials have been conducted.

they cannot be legally accessed or prescribed except in the context of a research study. Of the classic psychedelics, psilocybin, and specifically psilocybin-assisted psychotherapy (PAP), has been studied the most extensively as a potential treatment for disparate conditions (eg, treatment-resistant depression [TRD], end-of-life anxiety and depression, headaches, and pain).

What Are the Different Medical and Psychiatric Conditions Currently Being Investigated as Targets for Psilocybin Treatment?

The past 2 decades have seen a resurgence in research into the therapeutic potential of psychedelics, among them psilocybin. While there are now synthetic formulations of several classic psychedelics (including psilocybin, DMT, and 5-MeO-DMT) available for use in humans, psilocybin was the first to become available in a formulation that met good manufacturing practices required for human use by the US Food and Drug Administration. As a result, data on the therapeutic uses of psilocybin are the most abundant. Of note, psilocybin is usually administered along with other therapies, and therefore, most studies report the benefits of PAP. Of the therapeutic indications for which psilocybin has been studied, end-of-life/cancer-related distress, TRD, and major depressive disorder (MDD) have been studied the most extensively.[2] Before reviewing some of those studies in detail, it bears stating that while some of the studies included a placebo, considering the psychoactive effects of psilocybin, it is particularly challenging to blind participants to whether they are receiving active treatment. While the issue of blinding is not unique to psychedelic-related studies since there is often functional unblinding due to side effects in other clinical trials, reproducing effects like those of the psychedelic experience, as with psilocybin, does present a unique challenge and understandably raises concerns about the potential effects of expectation bias.

End-of-life/cancer-related distress. The second wave of research into psychedelics and psilocybin specifically began with studies of PAP to treat end-of-life–associated distress, including anxiety and depression, in patients with life-threatening cancer. To date, there have been 3 published studies of PAP for end-of-life/cancer-related distress, as shown in Table 1, but there are at least 6 ongoing clinical trials listed on https://clinicaltrials.gov. The first study[3] was a randomized, within-subject, double-blind, placebo-controlled, crossover study that investigated the safety and efficacy of PAP in the treatment of psychological distress associated with the existential crisis of a terminal disease. In total, 12 subjects with advanced-stage cancer and a diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder underwent 2 experimental sessions each in a crossover design, receiving an oral dose of active psilocybin (0.2 mg/kg) in 1 session and an oral dose of placebo (niacin 250 mg) in the other session. Depression scores dropped by almost 30% from the first session to 1 month after the second treatment session, but did not reach significance; however, the decrease in depression scores was sustained and became significant at the 6-month follow-up. There was also a significant reduction in trait anxiety, which was significant at 1 month after treatment and sustained at the 6-month follow-up.[3]

Subsequently, another crossover study[4] involving 29 participants with life-threatening cancer was published. However, the dose for active psilocybin was 0.2 mg/kg instead of 0.3 mg/kg, and both psilocybin and placebo (niacin) sessions were conducted in conjunction with psychotherapy. Interestingly, the single, moderate-dose psilocybin in this second study produced rapid, robust, and enduring anxiolytic and antidepressant effects that also led to decreases in cancer-related demoralization and hopelessness, improved spiritual well-being, and increased quality of life.[4] Prior to crossover, among those who received psilocybin first, 83% showed a greater than 50% reduction in depression scores, and 58% showed a greater than 50% reduction in anxiety symptoms. After both groups received psilocybin, at the 6.5-month follow-up, 60%–80% showed a greater than 50% reduction in depression and anxiety symptoms. Also, at 6.5 months, both groups showed significant reductions in suicidal ideation and loss of meaning, which were sustained at long-term follow-up, on average 2.7 years after intervention.[5]

The third study[6] using PAP for end-of-life/cancer-related distress assessed 51 individuals with life-threatening cancer. It employed a randomized, double-blind, crossover trial, but the "placebo" was a low dose (1 or 3 mg/70 kg) of psilocybin, and the active treatment was a high dose of psilocybin (22 or 30 mg/70 kg). They

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Table 1.
Summary of End-of-Life/Cancer-Related Distress Clinical Trials

Condition	Study design	Sessions/doses	Psychological support	Placebo vs active comparator	Population	N	Summary of outcomes	Side effects reported
Cancer-related distress, depression, and anxiety (Grob et al[3])	Randomized, double-blind, placebo-controlled, crossover trial (RCT)	2 sessions: 1 active session (moderate-dose psilocybin 0.2 mg/kg); 1 placebo (niacin)	Psychological support offered throughout both sessions	Placebo-controlled, niacin	Individuals with cancer-related anxiety and depression	12	Significant reductions in anxiety and depression at 1 mo after active dose, which were sustained at 6-mo follow-up	There were no clinically significant adverse events with psilocybin
Cancer-related distress, depression, and anxiety (Ross et al[4])	Randomized, double-blind, placebo-controlled, crossover trial (RCT)	2 sessions: 1 active session (moderate-dose psilocybin 0.3 mg/kg); 1 placebo (niacin)	Psychotherapy used in conjunction with treatment during both experimental sessions	Placebo-controlled, niacin	Individuals with life-threatening cancer	29	Significant reductions in anxiety and depression at 6 wk after active dose, which were sustained at 6.5-mo follow-up, as well as at long-term follow-up	No serious adverse events occurred; in 2 cases, transient psychotic-like symptoms occurred
Cancer-related distress, depression, and anxiety (Griffiths et al[6])	Randomized, double-blind, comparator, crossover trial (RCT)	2 sessions: 1 very low dose (1 or 3 mg/70 kg) of psilocybin; 1 high dose (22 or 30 mg/70 kg) of psilocybin	Psychological support offered throughout both sessions	Active comparator (very low dose of psilocybin acting, 1 or 3 mg/70 kg)	Individuals with life-threatening cancer	51	Significant reductions in depression and anxiety 5 wk after psilocybin session, sustained at 6-mo follow-up	No serious adverse events; headache, nausea, and physical discomfort were transiently experienced by <20% of participants

Abbreviation: RCT = randomized-controlled trial.

found that in the group receiving high-dose psilocybin first, 92% of participants showed a greater than 50% reduction in depressive symptoms, and 60% were in remission 5 weeks following the high-dose administration. Similarly, 84% of participants in the low-dose psilocybin group showed a greater than 50% reduction in depressive symptoms, and 68% were in remission 5 weeks following the high-dose administration. For anxiety, greater than 50% reduction in anxiety scores was 76% and remission was 52% in the high-dose first group, and 80% and 60%, respectively, for the low-dose first group. These decreases in depression and anxiety as well as increases in quality of life, life meaning, and optimism were sustained at the 6-month follow-up.[6] Taken together, the results of these 3 studies show not only encouraging data regarding the safety and efficacy of psilocybin as treatment but also a therapeutic promise that warrants further investigation.

Major depressive disorder. Positive results in treating depressive symptoms in patients with life-threatening cancer made way for clinical trials using PAP to target depression. To date, there have been 5 clinical trials of PAP targeting depression, 3 for MDD and 2 for TRD, all published in the last 2 years.

Regarding MDD, the first study was a phase II, double-blind, randomized trial of escitalopram versus psilocybin[7] in which 59 individuals with long-standing mild-to-moderate depression underwent treatment with either psilocybin or escitalopram and psychotherapy, which they referred to as psychological support. Patients were assigned in a 1:1 ratio to ingest 2 separate doses of 25 mg of psilocybin 3 weeks apart plus 6 weeks of placebo (psilocybin group, n = 30) or 2 separate doses of 1 mg of psilocybin 3 weeks apart plus 6 weeks of daily oral escitalopram (escitalopram group, n = 29; starting dose of 10 mg, with the option to escalate the dose to 20 mg at 3 weeks). The study[7] found that while PAP was well tolerated, the difference between psilocybin and escitalopram on the primary depression outcome was not significant.

A second study[8] of PAP targeting MDD provided more encouraging data. The study was a randomized, waiting-list controlled trial with 27 participants diagnosed with MDD. In this trial, participants underwent 2 psilocybin sessions 3 weeks apart (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg) in the context of supportive psychotherapy, and they were randomized to begin treatment right away or after an 8-week delay.[8] They found that regardless of which group they were in, 71% of the participants showed a greater than 50% reduction in depression scores 1 week and 4 weeks after the second dose of psilocybin, and 58% of participants were in remission 1 week after the second dose, which decreased to 54% in remission at 4 weeks.[8]

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Table 2.

Summary of Clinical Trials for Major Depressive Disorder

Condition	Study design	Sessions/doses	Psychological support	Placebo vs active comparator	Population	N	Summary of outcomes	Side effects reported
MDD (Carhart-Harris et al[7])	Randomized, double-blind trial psilocybin vs escitalopram (RCT)	Psilocybin group: 2 separate doses of 25 mg of psilocybin (3 wk apart), plus 6 wk of placebo Escitalopram group: 2 separate doses of 1 mg psilocybin (3 wk apart) plus 6 wk of daily oral escitalopram	Psychological support offered throughout both sessions	Active comparator was escitalopram, placebo used in the psilocybin group during 6-wk period and very low dose (1 mg) of psilocybin used in the escitalopram group during 2 psilocybin sessions	Individuals with MDD	30	No significant difference in antidepressant effect	No serious or unexpected adverse events occurred; incidence of nonserious, expected adverse events was similar
MDD (Davis et al[8])	Randomized, waiting-list, controlled trial, 2 groups: immediate and delayed wait list treatment condition (RCT)	Both groups received 2 sessions of moderate psilocybin doses in 2 sessions 3 wk apart (session 1 = 20 mg/70 kg, session 2: 30 mg/70 kg), immediately or after an 8-wk delay	Both groups received supportive psychotherapy during psilocybin sessions	No placebo used, waiting-list controlled study	Individuals with MDD	27	71% of participants had over 50% reduction in symptoms at 1-wk and 4-wk follow-up after the second dose; 58% were in remission at 1 wk and 54% were in remission at 4 wk after the second dose	No serious adverse events; a transient increase in blood pressure that exceeded the protocol criteria occurred during 1 session, but no medical intervention was needed
MDD (Raison et al[9])	Randomized, double-blind, placebo-controlled, crossover trial (RCT)	A single session; psilocybin group: 1 single 25-mg dose of synthetic psilocybin, niacin group: a 100-mg dose of niacin	Both groups received psychological support during the sessions, no psychotherapy	Placebo-controlled (niacin)	Individuals with MDD	51	Psilocybin treatment was associated with 3-fold greater reduction in depression scores compared to the niacin group on day 8 and day 43	Psilocybin was generally well tolerated, with most adverse events being of mild or moderate severity and generally limited to the acute dosing period

Abbreviations: MDD = major depressive disorder, RCT = randomized-controlled trial.

The third and most recently published clinical trial targeting MDD was a phase II, randomized, placebo-controlled, 6-week trial with 104 participants.[9] Participants were randomized in a 1:1 ratio to receive a single 25-mg dose of active psilocybin (n = 51) or the placebo niacin (n = 53). At 8 days following psilocybin administration, participants in the psilocybin group showed a nearly 3-fold greater reduction in depression scores compared with the niacin treatment group, and this was sustained at day 43. Additionally, 42% of participants in the psilocybin group showed sustained reductions greater than 50% in depressive symptoms on day 43 compared to only 11% in the niacin group.[9]

Despite the small number of studies that have investigated the therapeutic potential of PAP for MDD, and 1 study even finding no benefit over a traditional antidepressant, taken together, the data suggest that PAP is safe and well tolerated, and there are some initial promising results about the efficacy of PAP as a novel intervention for MDD (Table 2).

Treatment-resistant depression. The other 2 studies targeting depression with PAP focused on TRD, a subset of MDD in which patients do not respond to traditional and first-line therapeutic options.[10] Given the burden to individuals and society, and the few effective treatments for TRD, there is a huge need for novel treatments for TRD.

The first study[11] using psilocybin-assisted therapy to target TRD was an open-label, feasibility study of 20 participants with moderate-to-severe TRD who underwent 2 sessions of PAP in a supportive setting (active psilocybin doses of 10 and 25 mg, 7 days apart). Psilocybin was well tolerated by all patients, and no serious adverse events occurred. One week after psilocybin administration, 67% of participants were in remission, and 58% showed a greater than 50% reduction in depression symptoms at 3 months.[11] While it is important to note that open-label trials have their limitations with concerns about expectation bias, this initial study[11] with a TRD population showed tolerability and rapid symptom improvement after just 2 psilocybin treatment sessions, paving the way for future trials.

Yielding comparable promising findings, this was followed up with a double-blind, randomized trial of 233 participants with TRD who underwent a single

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Table 3.

Summary of Clinical Trials for Treatment-Resistant Depression

Condition	Study design	Sessions/doses	Psychological support	Placebo vs active comparator	Population	N	Summary of outcomes	Side effects reported
TRD (Carhart-Harris et al[11])	Open-label, within-subject, feasibility study	2 sessions of psilocybin (10 mg vs 25 mg) 7 d apart	Supportive psychotherapy	No placebo	Individuals with TRD	20	Depressive symptoms markedly reduced 1 wk after high-dose treatment, and results remained positive at 3- and 6-mo follow-up	No serious or unexpected adverse events occurred
TRD (Goodwin et al[12])	Double-blind RCT, 3 groups	1 single session of psilocybin, 3 groups: 1 mg (comparator), 10 mg (low dose), 25 mg (moderate/high dose)	Supportive psychotherapy was included in all groups	Comparator (very low-dose psilocybin, 1 mg)	Individuals with TRD	233 (79: 25 mg, 75: 10 mg, 79: 1 mg)	Participants who received the high dose of psilocybin had significant reductions in depression scores compared to the comparator group at 3 wk	Serious adverse events occurred in 5% of the high-dose group and 5% of the moderate-dose group

Abbreviations: RCT = randomized-controlled trial, TRD = treatment-resistant depression.

25-mg dose of PAP.[12] In the study,[12] 79 participants received a high dose (25 mg) of active psilocybin, 75 participants received a moderate dose (10 mg) of active psilocybin, and 79 participants received a comparator dose (1 mg) of active psilocybin in lieu of placebo. Three weeks following psilocybin administration, among participants who received 25 mg of psilocybin, 37% showed a greater than 50% reduction in depression symptoms, compared to 19% and 18% in the 10-mg and 1-mg groups, respectively, and so there was a significant reduction in depressive symptoms in the 25-mg group compared to the 1-mg comparator group but not between the 10-mg group and the comparator group. Common and expected adverse events occurred in 179 of 233 participants (77%) and included headache, nausea, and dizziness. Suicidal ideation or behavior or self-injury occurred in all dose groups.[12] Additionally, serious adverse events occurred in 4 participants (5%) in the 25-mg group and 4 participants (5%) in the 10-mg group; none of these events were reported on the day of psilocybin administration.[12]

More clinical trials investigating the therapeutic effect of psilocybin-assisted therapy for TRD are underway, but these first 2 studies show promising results for a population with a critical need for novel therapeutic options. Considering the frequency of serious adverse events that occurred in the double-blind TRD trial, 5% in the 10-mg group and 5% in the 25-mg group, there is also a need to continue gathering safety data to better understand the potential harms associated with PAP to inform good clinical decision making (Table 3).

Substance use disorders. There have also been several studies investigating PAP for substance use disorders (SUDs): 1 for nicotine dependence and 2 for alcohol use disorders (AUDs). The first study[13] investigating PAP for nicotine dependence was an open-label pilot design in which 15 psychiatrically healthy, nicotine-dependent individuals received a moderate (20 mg/70 kg) and a high (30 mg/70 kg) dose of active psilocybin (a third high or moderate dose was also optional) within a 15-week smoking cessation treatment protocol. Twelve of 15 participants (80%) showed 7-day point prevalence abstinence at the 6-month follow-up.[13] The success rate substantially exceeded commonly reported rates for other behavioral and/or pharmacologic therapies that target smoking cessation, which typically have a success rate lower than 35%.[13]

Regarding AUDs, there was an early open-label study of 10 volunteers with alcohol dependence who received orally administered psilocybin in 1 or 2 supervised sessions in addition to co-occurring therapy during the psilocybin sessions and therapy sessions devoted to preparation for, and "debriefing" from, the psilocybin sessions.[14] They found that the percentages of drinking days and heavy drinking days decreased by nearly 30% and by over 20%, respectively, between weeks 9 and 12 after psilocybin administration and were largely sustained at a 36-week follow-up.[14]

This was followed by a double-blind randomized clinical trial in 95 patients with an AUD, who received 12 weeks of manualized psychotherapy (motivation enhancement and cognitive-behavioral therapy [CBT]) and either psilocybin (n = 49) or diphenhydramine (n = 46) during 2-day medication sessions at weeks 4 and 8.[15] They found a significant decrease in the percentage of heavy drinking days for the psilocybin group compared to the diphenhydramine group, a nearly 2-fold greater decrease in the psilocybin group. They also found a significant decrease in the percentage of drinking

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Table 4.

Summary of Clinical Trials for Substance Use Disorders

Condition	Study design	Sessions/doses	Psychological support	Placebo vs active comparator	Population	N	Summary of outcomes	Side effects reported
SUD, nicotine (Johnson et al[13])	Open-label, pilot study	2 sessions: 1 moderate dose and 1 high dose	Treatment done in conjunction with a 15-wk therapeutic cessation program	No placebo	Psychiatrically healthy individuals with nicotine dependence	15	80% of participants were abstinent at 6-mo follow-up	No clinically significant adverse events requiring physician or pharmacologic intervention occurred
SUD, alcohol (Bogenschutz et al[14])	Open-label, proof-of-concept study	1 or 2 sessions of psilocybin (second session was optional): session 1 = 0.3 mg/kg, session 2 = 0.4 mg/kg	12 wk of manualized psychotherapy and CBT	No placebo	Individuals with a diagnosis of alcohol dependence	10	Following psilocybin treatment, percentage of drinking days and heavy drinking days significantly reduced between wk 9 and 12 and largely sustained at a 36-wk follow-up	There were no significant treatment-related adverse events
SUD, alcohol (Bogenschutz et al[15])	Randomized, double-blind, placebo-controlled trial (RCT), diphenhydramine group	2 sessions: first session = 25 mg/70 kg (psilocybin group) or 50 mg of diphenhydramine; second session: 30 mg/70 kg (psilocybin group) or 100 mg of diphenhydramine	12 wk of manualized psychotherapy and CBT	Diphenhydramine used as a placebo	Individuals with a diagnosis of alcohol dependence	49	There was a significant reduction in the percentage of heavy drinking days during and drinking days during the 32-wk period	There were no serious adverse events among participants who received psilocybin

Abbreviations: CBT = cognitive-behavioral therapy, RCT = randomized-controlled trial, SUD = substance use disorder.

days in the psilocybin group, with that group showing a 10% greater decrease compared to the diphenhydramine group.[15] Consistent with the promise shown by these early studies, there are currently 15 active studies looking at psilocybin for the treatment of SUDs (https://clinicaltrials.gov) (Table 4).

Other conditions. Other conditions that have been targeted more recently in early-stage clinical trials include obsessive-compulsive disorder (OCD), cluster headaches, and anorexia nervosa; some have more promising results than others. There was an open-label study[16] of PAP in 9 individuals with OCD that found it was well tolerated and that there were acute reductions in several core OCD symptoms in several subjects. Marked decreases in OCD symptoms were observed in all subjects during 1 or more sessions of varying doses of psilocybin (23%–100% decrease in OCD symptoms).[16] A new, first-of-its-kind trial with a double-blind, placebo-controlled, non-crossover design is being conducted now and is set to enroll 30 participants.[17]

Unfortunately, the results have been less promising for cluster headache, as an early randomized, double-blind placebo-controlled study of 15 participants showed that while psilocybin was well tolerated, there was no significant improvement.[18] Similarly, in a phase I, open-label study of PAP for anorexia nervosa with only 10 participants, while the safety data were promising, and there was a significant decrease in weight and shape-related concerns at the 1-month follow-up, these improvements did not persist through the 3-month follow-up assessment (Table 5).[19] Given the initial improvement, a follow-up study is underway with a larger sample. In addition to the variety of conditions mentioned previously, other active trials are investigating other targets for psilocybin interventions, including but not limited to type II bipolar disorder, attention-deficit/hyperactivity disorder, anxiety disorders, and binge eating disorder.[20–24]

How Might Psilocybin Improve the Quality of Life and Outcomes in Patients With Cancer?

As reviewed earlier, studies of PAP in cancer-related distress show rapid and significant reduction in symptoms of anxiety and depression.[3,4,6] Additionally, patients report that the psilocybin experience generates insights

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Table 5.

Summary of Clinical Trials for Psilocybin for Other Conditions

Condition	Study design	Sessions/doses	Psychological support	Placebo vs active comparator	Population	N	Summary of outcomes	Side effects reported
OCD (Moreno et al[16])	Pilot study	Up to 4 sessions of ranging psilocybin single doses: low (100 µg/kg), medium (200 µg/kg), high (300 µg/kg), and a very low dose (25 µg/kg) as a placebo	All participants received psychological support during the psilocybin sessions, no psychotherapy	Placebo was a low dose (25 µg/kg) of psilocybin	Individuals with OCD	9	Acute reductions in OCD symptoms in all participants	Except for 1 subject who experienced transient hypertension, no other significant adverse effects were observed
Cluster headache (Schindler et al[18])	Exploratory, double-blind, RCT study; 1:1 ratio groups, psilocybin vs placebo	3 sessions, each 5 d apart; psilocybin group: 0.143 mg/kg dose each session	Both groups received psychological support during the sessions, no psychotherapy	Placebo used was microcrystalline cellulose in all 3 sessions for the control group	Individuals with cluster headache	14	Efficacy outcomes were negative, owing in part to the small number of participants	Psilocybin was well tolerated with no unexpected or serious adverse events
Anorexia nervosa (Peck et al[19])	Phase I, open-label, feasibility study	One single dose of 25 mg of psilocybin	All participants received psychological support during the psilocybin session, no psychotherapy	No placebo	Females who met criteria for anorexia nervosa[25]	10	Psilocybin therapy is safe, tolerable, and acceptable for female anorexia nervosa; significant reductions in weight and shape concern at 1-mo follow-up, but no longer significant at 3-mo follow-up	No serious adverse events; 2 participants developed asymptomatic hypoglycemia at posttreatment, which resolved within 24 h

Abbreviations: OCD = obsessive-compulsive disorder, RCT = randomized-controlled trial.

during the altered state of consciousness that is achieved with moderate-to-high doses of psilocybin, allowing them the unique opportunity to confront and process difficult emotions related to their diagnosis, mortality, and even existential concerns.[3] Along those lines, patients also report seeing their circumstances from a different perspective, and with the help of psychological support, framing their lived experiences in a more positive context. Finally, many patients with cancer experience a heightened fear of death, and in the PAP trials for cancer-related distress, patients report a reduction in death-related fear and a more positive outlook overall on both life and death after treatment.[3,6]

What Are Side Effects and Drug-Drug Interactions to Consider With Psilocybin?

Just as the research on therapeutic benefits is in early stages, so too is our understanding of the harms (eg, side effects and drug-drug interactions). Of note, in controlled clinical trials in the second wave of research with psilocybin, it has been largely safe and well tolerated, and that is in part due to proper preparation for the psilocybin experience and safeguards in terms of setting for the experience. These factors are often referred to as "set and setting," short for the individual's mindset entering the psilocybin experience and the setting including environment and people among which the experience occurs. This has significant implications for patients who might want to experiment with psilocybin on their own, as it is important to remind them that the controlled preparation and environment that has yielded positive results is hard to replicate on one's own. During the psilocybin experience itself, there can be "bad trips," which are known as negative psychedelic experiences that consist of distressing emotions, thoughts, and/or sensations that negatively impact an individual's mental health. The likelihood of a bad trip increases without the proper set and setting.

Several side effects to consider with psilocybin have been well documented in clinical trials to date. These include transient psychological effects (including hallucinations, emotional intensity, mood alteration, confusion, anxiety, panic, and insomnia), as well as transient physiological effects (including headache, nausea, and dizziness). Studies[3,4,6–9,11–13,16,18,19] have reported the frequency of these transitory side effects as being present in 14%–77% of subjects. Additionally, there is documented risk of an increase in suicidal ideation and behaviors in a clinical trial of psilocybin for TRD; therefore, assessment of suicide risk following a psilocybin experience is critical.[26] Finally, there is risk of valvular heart disease, which is increased by 5-HT_{2B} agonism, for which psilocybin has an affinity; the extent of this risk had not yet been characterized.[27]

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Our knowledge of drug-drug interactions with psilocybin is inadequate, as most clinical trials of PAP have required patients to wean off their psychiatric medications before the trial. Given psilocybin's agonism at the serotonin 5-HT receptor, its potential interactions with other serotonergic agents are of concern. Recently, an exploratory study examined the safety, tolerability, and efficacy of psilocybin with an SSRI in 19 patients with TRD and found that most experienced some transitory side effects, not unlike other trial participants, and that overall psilocybin, even in conjunction with an SSRI, was generally well tolerated with good therapeutic efficacy.[26] Previously, in healthy participants, a small study[28] examining response to psilocybin (25 mg) after 14 days of pretreatment with escitalopram or a placebo found that escitalopram did not attenuate the subjective experiences associated with psilocybin and even decreased adverse drug effects, anxiety, adverse cardiovascular effects, and other adverse effects compared with placebo pretreatment. Also in healthy participants, buspirone,[29] chlorpromazine,[30] ketanserin,[31] and risperidone[32] have all been shown to attenuate the subjective effects of psilocybin.

What Are the Contraindications to Use of Psilocybin?

Several medical and psychological factors are contraindications to the use of psilocybin. Individuals with heart conditions (including high blood pressure or a history of heart problems) should avoid using psilocybin due to potential cardiovascular risks.[33,34] Pregnant and breastfeeding individuals should avoid taking psilocybin as well, as the potential for risks to the developing fetus/infant and for teratogenicity from psilocybin are unknown. Young age is another factor to consider, as psilocybin's potential risks on cognitive and emotional development in developing brains (including adolescents and young adults) are unknown. Finally, individuals with a history or family history of mental health conditions (such as bipolar disorder, schizophrenia, and other psychotic disorders) have been largely excluded from research, as psilocybin has the potential to cause the onset or worsening of these conditions. There has been a pilot study of psilocybin for 12 patients with type II bipolar depression with good effect, with no resulting manic symptoms or increase in suicidality, but the results are still preliminary.[35]

In Which Medical Settings Can Psilocybin Be Administered?

At present, psilocybin is a schedule I drug, and it remains an investigational new drug. As such, psilocybin for therapeutic purposes or within the medical framework can only be administered in the context of a clinical trial. Clinical trials are being carried out in a variety of medical settings (including hospitals, end-of-life care facilities, university research centers, and specialized treatment centers), which suggests universal adaptability of treatment settings for the administration of PAP.

What Happened to Mr D?

Upon reviewing his family history, Mr D learned that he had a first-degree uncle with bipolar disorder, which made him ineligible for current research studies of PAP for TRD. However, through the study team, he was referred to a ketamine treatment clinic, where he had a consultation and decided to proceed with ketamine treatment for his TRD, with good effect.

CONCLUSIONS

The past few decades have seen a resurgence of interest in the use of psychedelics, including psilocybin, for therapeutic purposes; early studies suggest promise for the use of psychedelics for a range of medical conditions, with the greatest evidence thus far for MDD and AUD. Considering the enthusiasm and media coverage, patients may be interested in psilocybin treatment; however, given their schedule I classification, the drug can only be accessed legally for therapeutic or medical purposes through participation in a clinical trial, if they qualify.

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