No. 21-70544

IN THE UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

ADVANCED INTEGRATIVE MEDICAL SCIENCE INSTITUTE, PLLC; DR. SUNIL AGGARWAL, M.D., Ph.D; MICHAL BLOOM; and ERINN BALDESCHWILER,

Petitioners,

v.

U.S. DRUG ENFORCEMENT ADMINISTRATION; MERRICK GARLAND, in his official capacity as Attorney General; and D. CHRISTOPHER EVANS, in his official capacity as Acting Administrator of the U.S. Drug Enforcement Administration,

Respondents.

BRIEF OF AMICI CURIAE END OF LIFE WASHINGTON, EVERGREENHEALTH, THE WASHINGTON STATE PSYCHOLOGICAL ASSOCIATION, A SACRED PASSING, AND PARTICIPATING END OF LIFE CARE CLINICIANS AND RESEARCHERS IN SUPPORT OF PETITIONERS AND SEEKING REVERSAL OF THE DEA FINAL AGENCY ACTION

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Fed. R. App. P. 26.1, amici curiae End of Life Washington, EvergreenHealth, The Washington State Psychological Association and A Sacred Passing disclose that none of these entities has a parent corporation and that no publicly held corporation owns 10 percent or more of stock, as they are all nonstock entities.

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I. IDENTITY AND INTEREST OF AMICI CURIAE[1]

A. Organizational Amici

Amicus curiae ***End of Life Washington ("EOLWA")***[2] is a non-profit organization in Washington State that provides direct service, community education, and advocacy to ensure that Washington residents have access to a full range of end-of-life options, including excellent palliative care and, for those who qualify and choose it, medical aid in dying. Founded in 1988, EOLWA believes that a peaceful death should be within everyone's reach and that no one should face intolerable suffering at the end of life. In 2008, EOLWA drafted and sponsored Initiative 1000 which was passed by Washington voters and became in 2009 the Washington Death with Dignity Act. RCW 70.245. EOLWA continues to implement this law by working closely with 90 to 95% of all Washingtonians who exercise their right to medical aid in dying. EOLWA upholds the right to the full range of end of life choices through advocacy, education, and support.

To those ends, EOLWA issued a policy statement in 2020, supporting access to psilocybin as a palliative treatment for terminally ill patients suffering from

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[1] This Brief of Amici Curiae is filed pursuant to Fed. R. App. P. 29(a) as all parties consent to its filing. No counsel for any party authored this brief in whole or part, and no person or entity other than amici, their members, or counsel, made any monetary contribution for the preparation or submission of this brief.

[2] https://endoflifewa.org/ (last visited 5/5/21).

debilitating depression and anxiety. *See* APP-17–21. The statement observes, "A terminal cancer diagnosis is well-known to produce anxiety and depression (including suicidal ideation) in a significant number of individuals" and cites studies showing that psilocybin therapy "is effective in relieving emotional and existential distress at the end of life for 65-85% of terminally ill people in clinical trials, when it's administered properly." The statement further notes there are "no lasting negative effects and many significant and enduring positive benefits" associated with psilocybin therapy. EOLWA advocates for terminally ill patients to have access to psilocybin-assisted therapy as one option to help relieve suffering at the end of life.

Amicus curiae ***EvergreenHealth*** is an integrated two-hospital healthcare system that was formed in 1972 as a public hospital district. The main campus is located in Kirkland, Washington and includes a 318-bed medical center. EvergreenHealth has been recognized by Healthgrades as one of America's 100 Best Hospitals for the past five years (2017-2021). EvergreenHealth partners with Seattle Cancer Care Alliance to deliver comprehensive cancer care at the Halvorson Cancer Center on the Kirkland campus, and also includes EvergreenHealth Home Care Services, which provides Home Health, Behavioral Health, Hospice, and Palliative Medicine care.

Every day, EvergreenHealth Hospice provides care to over 500 patients and their families residing in communities across King and Snohomish counties, as well as to patients and families who come to the 15-bed Hospice Care Center on the Kirkland campus. The Palliative Medicine services provides specialized consultation and management for patients with life-limiting illnesses in both inpatient and outpatient settings. As a state and national leader in end-of-life care, EvergreenHealth is committed to providing patients with access to the highest-quality comprehensive medical care available. This commitment is informed both by an understanding of the critical role of evidence-based medicine in end-of-life care, and by the recognition of the degree to which mental, emotional, and spiritual distress contribute to the suffering of patients with terminal illness. It is because of this deep commitment that EvergreenHealth advocates for terminally ill patients to have access to psilocybin-assisted therapy.

Amicus curiae the ***Washington State Psychological Association (WSPA)*** is a nonprofit scientific and professional organization founded in 1947. WSPA represents more than 600 members and affiliates, including the majority of psychologists holding doctoral degrees from accredited universities.

The mission of WSPA is to support, promote and advance the education, science and practice of psychology in the public interest. Indeed, WSPA is recognized at the national level of psychology for its dedication to promoting the

public interest. Whenever WSPA attempts to promote the public interest, it relies upon the most recent scientific evidence to establish what actions would enhance the mental and behavioral health of Washington citizens. With those principles in mind, WSPA fully supports efforts to make psilocybin available under Right to Try laws to help relieve non-physical suffering experienced by many people with a terminal illness.

Amicus curiae **A Sacred Passing (ASP)** offers accessible death and dying education to individuals, community associations and medical organizations. The mission of ASP is to educate, collaborate, and share ways to be supportive educational companions for those studying to be death companions, death doulas, and for those who are dying and for those caring for them. ASP offers education both online and in-person, and the crew is primarily located in Duwamish tribal land (or Seattle, WA). A Sacred Passing's mission is to guide and assist people towards a more conscious dying experience, while honoring their individual autonomy.

A Sacred Passing advocates, alongside End-of-Life Washington (EOLWA), *et al.*, for terminally ill patients to have access to psilocybin-assisted therapy. A Sacred Passing works in communities to actively dismantle systems of power and oppression as they present in dying and death through providing relevant, factual and accessible education, non-medical care and advocacy, ensuring the inclusion of peoples from systematically marginalized communities. Our long term goal is to

deepen partnerships with medical practitioners and other community groups to provide care to people in their dying that speaks to what they want, elevating a return to whole person, community supported care. It is for all of these reasons that we advocate on behalf of an individual's "Right to Try," as codified in both federal and state law. *See* 21 U.S.C. § 360bbb, *et seq.*; RCW 69.77, *et seq.* In 2017, the Washington state legislature enacted its "Right to Try" legislation and correctly noted that terminally ill patients "should be permitted to pursue the preservation of their own lives by accessing available investigational drugs," and that decisions about the use of available investigational drugs should be made by each individual person with the consultation of their health care provider.

B. Individual Amici

The following individual amici are all distinguished end-of-life clinicians and researchers who join with the organizational amici to support the rights of terminally ill patients to access psilocybin-assisted treatment under the federal and Washington state Right To Try laws:

- ***Ira Byock, M.D.***, palliative care physician and Active Emeritus Professor of Medicine and Community & Family Medicine of the Dartmouth Geisel School of Medicine;

- ***Nick Gideonse, M.D.***, Associate Professor of Family Medicine, Medical Director, MAT Program and Kindred Hospice, Oregon Health & Science University Family Medicine at Richmond;
- ***Roland R. Griffiths, Ph.D.***, The Oliver Lee McCabe, III Professor in the Neuropsychopharmacology of Consciousness; Director, Center for Psychedelic and Consciousness Research; Professor, Departments of Psychiatry and Neuroscience, Johns Hopkins University School of Medicine;
- ***Matthew W. Johnson, Ph.D.***, The Susan Hill Ward Professor of Psychedelics & Consciousness Research, Johns Hopkins University School of Medicine, Department of Psychiatry and Behavioral Sciences;
- ***Mikhail Kogan, M.D.***, Medical Director, George Washington Center for Integrative Medicine, Associate Professor of Medicine, Associate Director of Geriatrics Fellowship, George Washington University, Founder and Executive Director of AIM Health Institute, 501(c)(3) organization aimed at providing whole health and integrative care for vulnerable and Medicaid recipients of greater D.C. area;
- ***Timothy Quill, M.D., FACP, FAAHPM***, Professor of Medicine, Psychiatry, Medical Humanities and Nursing, University of Rochester Medical Center; and

- ***Lisa R. Yeager MSW, LICSW, CPTR***, Washington State palliative care social worker.

II. INTRODUCTION

In *Advanced Integrative Medical Science Institute, PLLC, et al., v. U.S. Drug Enforcement Administration, et al.,* the Petitioners seek review of the Final Agency Action by the U.S. Drug Enforcement Administration ("DEA") that it had "no authority to waive" any of the requirements of the Controlled Substances Act ("CSA") to accommodate both Washington state and federal legislation allowing for the use of any medication, including those listed in Schedule I of the CSA, under certain very limited circumstances. *See* RCW 69.77, *et seq.*; 21 U.S.C. § 360bbb, *et seq.* (collectively, "Right To Try" or "RTT"). As Petitioners argue, the DEA's interpretation undermines the purpose of state and federal Right To Try laws, raises significant constitutional concerns, and is arbitrary and capricious. *See generally,* Petitioners' Opening Brief.

This Brief describes the practical and policy impacts of the DEA Final Agency Action. As a practical matter, the DEA's position is a complete barrier to the Right To Try medications listed in Schedule I of the CSA – even when those medications would otherwise meet the stringent criteria for terminally ill patients to use them under Right To Try. This virtually nullifies, without authority, state and federal Right To Try laws, when patients seek to use psilocybin. If the DEA does not create

a waiver or other functional pathway for manufacturers to distribute and for physicians to safely and appropriately administer Schedule I medications that satisfy the stringent requirements of the Right To Try statutes, terminally ill patients will be forced to endure unnecessary harm that the statutes were designed to prevent.

Psilocybin is a Schedule I controlled substance that is a highly promising palliative care medication. In recent years, multiple well-controlled studies demonstrated "significant efficacy and few adverse side effects" when psilocybin was administered as part of a therapy protocol for seriously ill patients. *See* APP-22–26, Ira Byock, M.D., FAAHPM, *Taking Psychedelics Seriously,* 21 Journal of Palliative Medicine 4 (2018) (hereinafter "Byock").[3] Psilocybin therapy may offer immediate and sustained relief to terminally ill patients for whom conventional psychiatric treatment and medications have been unable to sufficiently treat the depression and anxiety associated with an incurable disease. As Dr. Byock wrote, ***this relief may be life-extending.*** *Id.,* APP-23. Right To Try laws were designed to enable terminally ill patients to try potentially life-sustaining medications that would otherwise be unavailable, whether the medications sought treated a patient's physical or mental health.

[3] The medical articles, studies, position statement for EOLWA and declarations of terminally ill patients Susan Patz and John Borrow, M.D., cited in this brief are attached in the Appendix for the convenience of the Court.

The DEA's action here blocks all access under the Right To Try to highly promising psilocybin treatment. As a practical matter, manufacturers will not produce or distribute psilocybin for treatment, nor will physicians be able to administer psilocybin therapy, without a path to do so that protects them from prosecution. Although state and federal Right To Try laws were enacted to provide such a path, the threat of possible prosecution or sanctions by the DEA for producing, distributing or administering a Schedule I drug is so great that the DEA's Final Agency Action effectively eliminates this treatment option under Right To Try. Nor is the DEA's preferred approach – that physicians interested in administering psilocybin therapy do so as a "researcher" – a feasible alternative. Amici and their constituents, all terminally ill patients and the palliative care providers who treat them, cannot wait for months, if not years for more research studies to be established, just so that these drugs may be administered. Nor can they easily access the treatment under the FDA's existing Expanded Use program; Right To Try was specifically designed to provide an alternative option for accessing investigational drugs to other FDA pathways including Expanded Use. Terminally ill patients should be able to receive this promising and possibly life-extending treatment ***without delay***, through the streamlined access provided by Right To Try.

III. ARGUMENT

A. Congress, and the State of Washington Opened the Door to Investigational Treatment with the Right To Try.

"A fair reading of legislation demands a fair understanding of the legislative plan." *King v. Burwell,* 576 U.S. 473, 498, 135 S. Ct. 2480 (2015). With the Right To Try, Congress sought to eliminate barriers to treatment with investigational drugs for terminally ill patients. As a result, Right To Try "allows use of unapproved medical products by patients diagnosed with a terminal illness in accordance with State law," free from federal prosecution, provided that certain conditions are met. 21 U.S.C. § 360bbb-0a. The Food and Drug Administration ("FDA") described the law's purpose:

> This law provides a new pathway for patients to request, and manufacturers or sponsors to choose to provide, access to certain unapproved, investigational drugs, including biological products, for patients diagnosed with life-threatening diseases or conditions (as defined in § 312.81 (21 CFR 312.81)) who, as certified by a physician, have exhausted approved treatment options and who are unable to participate in a clinical trial involving the investigational drug.

APP-274–276*,* 85 Fed. Reg. 44803, 44805. The Right To Try placed the decision-making regarding access to investigational drugs, in the hands of the terminally ill patient and their treating provider, under stringent conditions. *See id.; see also* APP-27–28, https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try (last visited 5/9/21). When those strict conditions are met, the Right To Try is permitted, without further government intervention.

Congress amended the Right To Try into the existing Food, Drug and Cosmetics Act ("FDCA"). Importantly, Congress prohibited any part of the Controlled Substances Act from being "construed as in any way affecting, modifying, repealing or superseding the provisions of the [FDCA]" ***including the Right To Try***. *See* 21 U.S.C. § 902. Congress's determination that the Right To Try prevails over any part of the CSA is presumed to be deliberate. *United States v. Motamedi*, 767 F.2d 1403, 1406 (9th Cir. 1985).

Similarly, the State of Washington concluded that "[p]atients who have a terminal illness do not have the luxury of waiting until an investigational drug, biological product or device receives final approval from the United States Food and Drug Administration." RCW 69.77.010. The law was designed to permit use of unapproved medications without any approval from the FDA. *See* APP-29–31, Final Bill Report on SSB 5035 (2017).[4] Importantly, the Washington Legislature did not exclude Schedule I medications from the definition of "investigational products" covered by the Washington Right To Try law. *See* RCW 69.77.020(4) ("'Investigational product' means a drug, biological product, or device that has successfully completed phase one and is currently in a subsequent phase of a clinical trial approved by the United States Food and Drug Administration assessing the

[4] http://lawfilesext.leg.wa.gov/biennium/2017-18/Pdf/Bill%20Reports/Senate/5035-S%20SBR%20FBR%2017.pdf?q= 20210511123405 (last visited 5/11/21).

safety of the drug, biological product, or device under section 505 of the federal Food, Drug, and Cosmetic Act, 21 U.S.C. Sec. 355").[5] Psilocybin is covered by both the federal and Washington State Right To Try laws.

B. Psilocybin Therapy is a Promising Palliative Care Treatment that Qualifies for Use Under Right To Try.

Palliative care providers deliver specialized medical treatment to people living with serious, and often incurable, illness. The focus of palliative care is to improve the quality of life for patients and provide relief from the symptoms and stress associated with debilitating conditions. Palliative treatment seeks to provide relief from pain, anxiety and depression, and, in particular, the existential distress associated with a terminal illness. As many as 40% of cancer patients experience such clinically significant psychological distress that they meet the criteria for a mood disorder. *See* APP-32-48, Griffiths, et al., *Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life threatening cancer: A randomized double-blind trial,* 30 JOURNAL OF PSYCHOPHARMACOLOGY 1181-1197 (2016) (hereinafter "Griffiths"). Addressing the anxiety and depression of terminally ill patients is a key component of palliative treatment.

[5] Some other states specifically excluded Schedule I drugs from the scope of their Right To Try statutes. *See, e.g.,* Mo. Rev. Stat. § 191.480(2).

The tools that palliative care providers have to treat serious and debilitating mental health symptoms include psychological counseling and psychiatric medications. For some terminally ill patients, however, these conventional interventions are insufficient or ineffective to provide relief. *See* Byock, APP-23. Psychiatric medication may take too long to become effective, or may be determined to be ineffective. *Id.* Psychiatric medications may also have significant side effects that may be a serious concern for terminally ill patients. *Id.* Many palliative care providers look to psilocybin as a promising alternative when conventional treatment is not effective or appropriate. APP-49–51, Kelmendi, *et al.,* "*The role of psychedelics in palliative care reconsidered: A case for psilocybin*," JOURNAL OF PSYCHOPHARMACOLOGY 1-3 (2016) (hereinafter "Kelmendi"). Indeed, a host of recent studies show that it may be a safe and effective option for certain patients when administered properly.[6]

[6] Although potential adverse effects of psilocybin are well documented, treatment with psilocybin can be safe and effective when standard safety guidelines are followed. *See* APP-68-85, Johnson, et al., *Human Hallucinogen Research: Guidelines for Safety,* 22(6) JOURNAL OF PSYCHOPHARMACOLOGY 603-620 (2008). These include screening patients for medical or psychiatric contraindication, psychological preparation of patients before psilocybin administration, psychological support of patients during and after a psilocybin session, and treatment supervised by an appropriately trained clinician familiar with psilocybin treatment. *Id.,* APP-73–81.

C. Recent Studies Demonstrate the Potential for Psilocybin Therapy to Aid Terminally Ill Patients

In 2016, a randomized double-blind trial evaluated the impact of a single dose of psilocybin treatment on depression and anxiety in patients with a form of life-threatening cancer. *See* APP-52–67, Ross, *et al.,* "Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial," 30 JOURNAL OF PSYCHOPHARMACOLOGY 1165-1180 (2016). No serious adverse events attributed to psilocybin were recorded. *Id.,* APP-62. The study concluded that even a single dose of psilocybin, administered under supportive conditions, was effective to decrease the symptoms of depression and anxiety, and to increase the quality of life of cancer patients. *Id.,* APP-62. Importantly for terminally ill patients, the effects were sustained at a review six months later. *Id.* In sum, the study revealed that even a single dose of psilocybin, administered in a supportive environment, can significantly improve the well-being of patients with a life-threatening disease. A second 2016 study revealed similar results. *See* APP-32-48, Griffiths.[7]

[7] Based upon these studies, psilocybin has been recommended for rescheduling under Schedule IV of the CSA. *See* APP-94–148, Johnson, et al., *The Abuse Potential of Medical Psilocybin According to the 8 Factors of the Controlled Substances Act*, NEUROPHARMACOLOGY 142 (2018).

Other studies confirm as much. In an earlier 2011 double-blind randomized controlled study, similar results were obtained, albeit with a smaller sample. APP-86–93, Grob, *et al.,* "*Pilot Study of Psilocybin Treatment for Anxiety in Patients with Advanced-State Cancer*," 68 ARCH GEN PSYCHIATRY, pp. 71-78 (2011). The participants experienced a significant reduction in anxiety at one and three months after the treatment. *Id.* No significant adverse events were identified. *Id.* In late 2020, a fourth randomized controlled study concluded that psilocybin therapy is effective at producing large, rapid, and sustained anti-depressant effects in patients with cancer and treatment-resistant depression. APP-149-157, Davis, *et al., Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial,* JAMA PSYCHIATRY (November 4, 2020) found at https://jamanetwork.com/journals/jamapsychiatry/fullarticle/2772630 (last visited 5/12/21). When the risks of psilocybin therapy are compared to the risks of conventional psychiatric medications, their safety profile appears to be quite strong. *See* Marks, Mason M., *Recent Development: Controlled Substance Regulation for the COVID-19 Mental Health Crisis,* 72 Admin. L. Rev. 649, 663-665 (Fall 2020) (hereinafter "Marks"). The "margin of safety" for psilocybin therapy is heightened because it is always administered with professional supervision according to a structured protocol. *Id.,* p. 665.

The reported benefits described in these studies are consistent with the reports from palliative care patients themselves. In a recent case study, four cancer patients described their experience with psilocybin treatment. *See* APP-158–163, Malone, *et al., Individual Experiences in Four Cancer Patients Following Psilocybin-Assisted Therapy,* 9 FRONT. PHARMACOL. 256 (April 3, 2018). Each described the different ways in which access to this treatment improved their lives and health. Each case study revealed decreased anxiety and increased sense of purpose in life after psilocybin treatment. *See, e.g.,* p. 4 (Tom: "I don't have a fear of death … I am more interested in life now than ever before"); p. 5 (Brenda: "I feel more contented and happy about my place in the world in all the things I'm doing"). Indeed, in the 2016 Griffiths study (APP-32–48), over two-thirds of the participants ranked the single dose of psilocybin therapy among the most meaningful experiences of their lives. Marks, p. 659.

D. Palliative Care Professionals Support the Use of Psilocybin Therapy under Right to Try laws.

Many palliative care providers are cautiously optimistic that psilocybin therapy will provide a critical tool missing from their toolbox – a treatment that will ease the anxiety and depression associated with the end of life. *See* APP-49–51 (Kelmendi). Many hope that this treatment will, in fact, extend the lives of their

patients by reducing suicidality and the desire for medical aid in dying.[8] This possibility unites palliative care providers who support and oppose "medical aid in dying" treatment. *See, e.g.,* APP-164-166, Timothy E. Quill, MD, MACP, FAAHPM, "Statement Supporting Oregon's Measure 34, the Psilocybin Service Initiative Enabling Access for Palliative Care in Terminally Ill Patients.". For example, Dr. Byock, a staunch opponent of medical aid in dying, wrote in 2018 that palliative care physicians should consider the therapeutic use of psychedelic medications, including psilocybin, for patients for whom conventional treatment has been unsuccessful:

> Palliative care clinicians and teams also encounter patients whose misery is rooted in emotional, social, existential, or spiritual distress. Cancer, heart failure, liver failure, and amyotrophic lateral sclerosis (ALS) or motor neuron disease are among the diseases that can result in a progression of personal losses: Of feeling in control. Of taking care of one's self. Of contributing to others. Of enjoyment. Of meaning and purpose. Ultimately, some ill people say they have lost any reason to go on living.
>
> People who are incurably ill and living with progressive disease-related disabilities can experience anxiety, depression, and demoralization. Therapy alone and drug treatments for such syndromes are often insufficient. Medications for depression may take weeks to become effective or prove ineffective. Antidepressants and anxiolytics carry side effects that can include mental slowing and confusion. These adverse effects are particularly common and hazardous in patients with advanced physical illness, who are also at risk of polypharmacy,

[8] Medical aid in dying, which has been legal in Washington since 2008, allows qualified, terminally ill adults to request a prescription for medication that will hasten their death after satisfying multiple strict requirements.

> multidrug interactions, and concomitant disequilibrium and falls. When nonphysical suffering persists despite prudent approaches, published, evidence-based guidelines are limited.

APP-23 (Byock). Dr. Byock predicted that use of psilocybin, in carefully supervised, structured settings, might ease the suffering of patients in this situation, and could extend their lives. Put simply, patients who feel less depressed and anxious about their terminal diagnosis, may live longer, either through improved mental and physical health or a possible delay in seeking medical aid in dying. *Id.,* APP-25 ("A person with severe depression, who has a coexisting serious, life-threatening physical condition, may feel that his or her quality of life is not worth living and may forgo arduous, but potentially life-saving treatments"); APP-167–176, Calder, Abigail E., "*Psilocybin and the Will to Live*," PSYCHEDELIC SCIENCE REVIEW (May 6, 2021) ("[A] cancer diagnosis increases someone's risk of suicide four-fold") (hereinafter "Calder"). For this reason, Dr. Byock advocates that psilocybin therapy be "legitimately cast as a ***right to try*** issue." *Id.* (emphasis added). By effectively decreasing depression and anxiety and increasing the desire for life in terminally ill patients, psilocybin treatment may have an even greater life-saving effect than other medications typically considered under the Right To Try laws. *See id.*

Similar opinions were elicited from a recent study of 17 palliative care experts. *See* APP-177–188, Beaussant, *et al., Defining the Roles and Research*

Priorities for Psychedelic-Assisted Therapies in Patients with Serious Illness: Expert Clinicians' and Investigators' Perspectives, JOURNAL OF PALLIATIVE MEDICINE (2020). The study found three consistent themes expressed by the experts: (1) there is a significant unmet clinical need for relief from depression and anxiety among patients with serious illness; (2) existing interventions (such as psychiatric medications and therapy) are limited and not effective for some; and (3) psilocybin therapy may have a rapid impact on reducing distress associated with a life-threatening disease. *Id.,* APP-182. And, as demonstrated by the individual Amici listed here, all distinguished and experienced clinicians and researchers, there is significant support for pursuing the use of therapeutic psilocybin by palliative care professionals.

E. Patients Need this Palliative Care Option.

Most importantly, patients facing the end of life have the right to try psilocybin treatment, since it may relieve suffering, improve the quality and prolong the quantity of their life. End of Life Washington represents the interests of these patients, including Susan Patz and James Borrow, M.D.

Like the patient Petitioners in this matter, Ms. Patz is a terminally ill patient who desperately seeks relief from her treatment-resistant depression and anxiety and is eager to try psilocybin. *See* ER-10–17, ER-18–23. Ms. Patz suffers from late-stage amyotrophic lateral sclerosis (ALS), known by many as Lou Gehrig's disease.

APP-11–16, Patz Decl., ¶ 3.[9] It is a fatal disease for which there is no cure and involves progressive and inexorable loss of a patient's bodily function and integrity, while their mental state remains fully intact. *Id.* Her prognosis is one to two years. *Id.*

Ms. Patz has experienced the kind of debilitating physical losses described by Dr. Byock that have now led to other serious psychological losses. *See* APP-23 (Byock). At first, she experienced some loss of physical control which has now spread to the point where she can no longer stand or walk. APP-12, Patz Decl., ¶ 4. This physical loss severely constrains Ms. Patz's life and she can no longer enjoy activities that gave her joy and satisfaction. *See id.,* ¶ 5. She can no longer garden, drive a tractor, swim, or cook, all activities about which she was passionate. *Id.* She has also lost her career as a cardiac care nurse which gave her a "tremendous sense of purpose." *Id.,* ¶ 6. Ms. Patz describes the depression she now experiences as

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[9] Consideration of similar declarations to those filed herein is often permitted. In *Webster v. Reproductive Health Services,* 492 U.S. 490, 109 S. Ct. 3040 (1989), an amicus brief filed with the Supreme Court included numerous declarations by women who had experienced legal and illegal abortions. More recently, the Ninth Circuit and U.S. Supreme Court considered amicus briefs containing such declarations of surviving family members of terminally ill individuals who desired to hasten their deaths. *See Compassion in Dying v. State of Washington,* 79 F.3d 790, 834 n. 126 (9th Cir. 1996), *rev'd, Washington v. Glucksberg,* 521 U.S. 702, 117 S. Ct. 2258 (1997); *Oregon v. Ashcroft,* 368 F.3d 1118 (9th Cir. 2004), *aff'd, Gonzales v. Oregon,* 546 U.S. 243, 126 S. Ct. 904 (2006). As in the above cases, the declarations filed here in the Appendix to the brief contain first-hand information by persons intimately familiar with the issues presented to the Court.

"constant and severe." *Id.* ¶ 7. She feels as if she has been at "rock bottom" for more than two and a half years and has contemplated suicide more than once. *Id.* She has tried conventional psychiatric treatment and medications but they have not provided her with sufficient relief. *Id.,* ¶ 13.

Ms. Patz does not want to continue in this manner, and she would like to try psilocybin treatment:

> I want to experience joy during the time I have left. I want to enjoy the company of my family and friends. I want to appreciate my home and my animals. I want to find pleasure in things like reading and food again. I want to stop crying so much.
>
> …
>
> I want to try this treatment. I don't want to keep living in this deep, dark place where my mind has been stuck for the past two-and-a-half years. I don't want to spend the last year or two of my life feeling isolated, depressed, and suicidal. I am desperate to try something that will work, something that will enable me to experience joy and pleasure again. ***If the Right-to-Try laws don't allow someone like me the chance to try something that may help alleviate my suffering, then what good are they***?

Id., ¶¶ 12, 14 (emphasis added). Ms. Patz is not seeking psilocybin treatment for recreational purposes. She advocates for its use in a controlled setting, under the care of her palliative care clinician, with proper protocols for patients like her at the end of life, for whom conventional treatment has been unsuccessful. *Id.,* ¶ 14. That is the precise situation Right To Try laws were designed to address.

Similarly, Dr. Borrow, a retired radiologist, is diagnosed with Stage 4 Leimyosarcoma, a rare cancer that attacks the smooth muscles that line organs throughout the body. APP-6–10, Borrow Decl., ¶ 4. Dr. Borrow's condition is also terminal. *Id.,* ¶ 4. Dr. Borrow experiences significant, debilitating anxiety related to his condition. *Id.,* ¶ 5 ("At times I feel hammered and overwhelmed by this unexpected diagnosis"). As a physician he read with great interest the recent studies and articles on psilocybin and believes that it is a medical treatment that will provide him with significant benefit: "I am eager to try this treatment, as I believe it may help me to integrate my terminal diagnosis with what time I have left so that I can live the rest of my life to the fullest, as well as provide relief from the anxiety I experience." *Id.* Dr. Borrow hopes that the treatment will improve his life so significantly that his life will be prolonged and he may avoid medical aid in dying. *Id.,* ¶ 6. Dr. Borrow has tried to participate in research studies of psilocybin but has not identified any study for which he is eligible. *Id.,* ¶ 7

The reasons Dr. Borrow and Ms. Patz seek psilocybin treatment echo those of the patient Petitioners, both of whom are diagnosed with serious, advanced, and life-threatening conditions. As Petitioner Baldeschwiler wrote, "[t]he prospect of dying soon and not being here to watch my children grow up, and to nurture them to adulthood causes me severe anxiety and depression, which conventional therapy has not ameliorated." ER-19, ¶ 4. "It is my hope that therapy facilitated with psilocybin

will allow me to obtain relief from the debilitating anxiety and depression I endure." ER-20, ¶ 9. Petitioner Bloom seeks psilocybin treatment for similar reasons: "I have experienced a lot of suffering from unrelieved anxiety and depression" that she believes "psilocybin assisted therapy could improve." ER-12–13, ¶¶ 7, 9. The organizational amici count as their constituents many other patients who would consider psilocybin therapy under Right To Try, should the DEA's Final Agency Action be reversed and a clear and timely path for terminally ill patients be established for this treatment.

F. All Requirements of Right To Try Are Met By Petitioners.

There is no dispute that psilocybin therapy, as proposed by Dr. Aggarwal, meets the requirements of Right To Try. ***First,*** the medication has completed an FDA-approved Phase I clinical trial. *See* 21 U.S.C. § 360bbb-0a(a)(2)(A); APP-189–209, Michael W. Jann, *Psilocybin Revisited: The Science Behind the Drug and Its Surprising Therapeutic Potential*, 38 PSYCHIATRIC TIMES 3 (Mar. 9, 2021). ***Second,*** the drug is not approved or licensed under the FDCA or the Public Health Services Act. *See* 21 U.S.C. § 360bbb-0a(a)(2)(B). ***Third,*** psilocybin is under investigation in a clinical trial and is the subject of an active IND application. *See* 21 U.S.C. § 360bbb-0a(a)(2)(C); *see* APP-210–273, Psilocybin Investigator's Brochure, Usona Institute, https://www.usonainstitute.org/wp-content/uploads/2020/08/Usona_Psilocybin_IB V3.0_08.31.2020_cc.pdf, p. 10 (last

visited 5/11/21). And ***fourth,*** the medication is actively under development and production, and not subject to a clinical hold.[10] *See* 21 U.S.C. § 360bbb-0a(a)(2)(D). *See also* RCW 69.77.020(4).

Nor is there any dispute that the patient Petitioners are "eligible" under the Right To Try. *See* 21 U.S.C. § 360bbb-0a(a)(1); ER-10–17, ER-18–23. Petitioners Bloom and Baldeschwiler are terminally ill cancer patients who seek treatment with psilocybin therapy from Dr. Aggarwal and who have completed the Right To Try Informed Consent document required under RCW 69.77.020. *See* ER-15–17; ER-22–23; Dkt. No. 9-2, ¶ 9. Dr. Aggarwal is willing to obtain any required authorization identified by the DEA that is consistent with the directives of Right To Try and the time and treatment constraints of his patients. ER-27, ¶ 10. As explained below, the DEA's suggestion that Dr. Aggarwal obtain a waiver from prosecution as a "researcher" is unworkable, and inconsistent with Right To Try laws, which allow for ***therapeutic use*** of investigational drugs.

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[10] In any event, under Right To Try, the manufacturer of psilocybin, not the FDA or DEA, determine if these criteria are met. APP-274-276, 85 Fed. Reg. 44,803, 44805 ("[A] manufacturer or sponsor is in the best position under the Right To Try Act to determine if an investigational drug meets these criteria…. FDA is not proposing to make determinations about whether a particular investigational product is an eligible investigational drug under the Right To Try Act").

G. The DEA's Proposed Researcher Waiver is Not An Alternative To Right To Try.

In response to Dr. Aggarwal's request for authorization or registration from the DEA to obtain psilocybin, the DEA refused to recognize a path for legal possession of psilocybin pursuant to the Right To Try laws. Instead, the DEA suggested that Dr. Aggarwal apply for a DEA Schedule I researcher registration to conduct research with psilocybin. ER-9, citing to 21 U.S.C. § 823(f), 21 C.F.R. §§ 1301.18, .32. If granted, the DEA advised that Dr. Aggarwal could then petition for a grant of an exemption from prosecution. *Id.,* citing to 21 C.F.R. § 1316.24(b). That is the only option provided by the DEA for Dr. Aggarwal to support his patients' efforts to use psilocybin without threat of prosecution.

The DEA's approach would defeat both the letter and the spirit of the Right To Try laws. As noted above, the purpose of the Right To Try was to streamline the process for terminally ill patients to obtain investigational medications for therapeutic use without governmental interference. *See* § III.A., *supra.* The DEA's Final Agency Action, however, directs Dr. Aggarwal to obtain multiple governmental authorizations as a "researcher" before he can support his patients' treatment with psilocybin under Right To Try. Put simply, the DEA's approach would re-impose government regulation on the Right To Try process, despite the directives of both Congress and the Washington Legislature. This defeats the

explicit purpose of Right To Try – to create a timely, informed and easily accessible pathway to investigational medication outside of the DEA and FDA.

DEA's preferred approach is akin to a "Single-Patient IND" application[11] for treatment for psilocybin, similar to what was tried in the 1990s related to compassionate use of marijuana. *See* Pet. Opening Brief, p. 24. The FDA/DEA "work around" was ineffective then, (*see id.*) and will not work to provide terminally ill patients with timely and effective access to psilocybin treatment now. The DEA's suggestion would force Dr. Aggarwal through two time-consuming bureaucratic procedures, during which he would have to reshape the therapeutic use of psilocybin for his patients into a "research" framework. This is the very problem that Congress sought to fix with Right To Try.

Nor could Dr. Aggarwal and his patients with terminal cancer simply join existing research studies in order to obtain psilocybin treatment. There are few existing studies of psilocybin that are actively recruiting participants in the United States. *See* APP-277–279 (identifying clinical studies of psilocybin currently recruiting participants in the United States) found at: https://clinicaltrials.gov/ct2/results?term=psilocybin&recrs=a&map_cntry=US (last visited 5/18/21). Presently, none are in Washington state. *Id.* Even if there were an

[11] "IND" stands for Investigational New Drug.

available, accessible study, the Petitioner patients may not meet the particular characteristics required for the study. *See* APP-280-299, *Expanded Access and Right to Try: Access to Investigational Drugs,* Congressional Research Service, March 16, 2021, p. 3.

The only possible alternative to Right To Try for Petitioners is through the FDA's Expanded Access Program. *See* APP-300-332, "Investigational Drugs: FDA and Drug Manufacturers Have Ongoing Efforts to Facility Access for Some Patients," U.S. General Accounting Office, Report to Congressional Committees, September 2019, p. 2. Under that program, a physician must be approved by the DEA as a Schedule I researcher and then be approved by an Institutional Review Board and the FDA. *See* APP-333-337, Usona Institute, "Expanded Access Policy: Single-Patient Expanded Access," https://www.usonainstitute.org/expandedaccess/ (last visited 5/18/21). Dr. Aggarwal's experience with Expanded Access is revealing. He had previously sought a Schedule I medication for patients in urgent need through Expanded Access. ER-27, ¶ 10. Despite his efforts, no access to the medication was provided. "In my experience, Expanded Access was an unworkable process for my terminally ill patients with an urgent need for an eligible investigational drug." *Id.* Neither Dr. Aggarwal nor his terminally ill patients have the time necessary to navigate these complex administrative procedures at the very end of life. And, in any event, Congress intended Right To Try as an alternative

avenue for access to investigational drugs. If upheld, the DEA's final agency action would foreclose the path Congress created with Right To Try by forcing physicians back into the unworkable Expanded Access program.

H. The DEA's Action May Have the Unintended Effect of Shortening Patients' Lives.

In Washington, terminally ill patients are empowered to seek medical aid in dying in order to advance the time of death. *See* RCW 70.245, *et seq.* Under Washington law, patients like the Petitioners, Dr. Borrow and Ms. Patz may request, obtain and self-administer controlled substances to hasten their death. RCW 70.245.020. Some may seek aid in dying medications because they cannot find relief from the depression and anxiety they experience related to their terminal condition. *See, e.g.,* APP-15, Patz Decl., ¶¶ 12, 14. The Washington Legislature approved Right To Try to address this very situation – those times when terminally ill patients do not have the "luxury of waiting" for governmental approvals. *See* RCW 69.77.010. In sum, if Petitioners can take controlled substances to hasten their death, they should also be authorized access to controlled substances that are shown to relieve anxiety and depression, so that they may live their lives to the fullest while they can.

IV. CONCLUSION

This Court should direct the DEA that the Controlled Substances Act cannot "affect, modify, repeal, or supersede" the Right To Try. As requested by Petitioners,

the DEA's Final Agency Action must be overturned and the case remanded to the DEA, to establish a functional pathway for terminally ill patients and their palliative care providers to access psilocybin therapy without threat of prosecution.

RESPECTFULLY SUBMITTED this 21st day of May, 2021.

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CERTIFICATE OF COMPLIANCE FOR BRIEFS

9th Cir. Case No. 21-70544

I am an attorney for Amici Curiae End of Life Washington, EvergreenHealth, The Washington State Psychological Association, A Sacred Passing, and Participating End of Life Care Clinicians and Researchers.

This brief contains **6,441 words,** excluding the items exempted by Fed. R. App. P. 32(f). The brief's type size and typeface comply with Fed. R. App. P. 32(a)(5) and (6).

I certify that this Amici Brief complies with the word limit of Fed. R. App. P. 29(a)(5), Cir. R. 29-2(c)(2), or Cir. R. 29-2(c)(3).

DATED: May 21, 2021.

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CERTIFICATE OF SERVICE

I hereby certify on May 21, 2021, I electronically filed this Amicus Brief with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the appellate CM/ECF System. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

DATED: May 21, 2021, at Seattle, Washington.

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No. 21-70544

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FOR THE NINTH CIRCUIT

ADVANCED INTEGRATIVE MEDICAL SCIENCE INSTITUTE, PLLC; DR. SUNIL AGGARWAL, M.D., Ph.D; MICHAL BLOOM; and ERINN BALDESCHWILER,

Petitioners,

v.

U.S. DRUG ENFORCEMENT ADMINISTRATION; MERRICK GARLAND, in his official capacity as Attorney General; and D. CHRISTOPHER EVANS, in his official capacity as Acting Administrator of the U.S. Drug Enforcement Administration,

Respondents.

APPENDIX (Volume 1 of 1)
to Amici Curiae Brief of End of Life Washington, *et al.*

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CERTIFICATE OF SERVICE

I hereby certify on May 21, 2021, I electronically filed this Appendix to Amici Brief of EOLWA, et al., with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the appellate CM/ECF System. I certify that all participants in the case are registered CM/ECF users and that service will be accomplished by the appellate CM/ECF system.

DATED: May 21, 2021, at Seattle, Washington.

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DECLARATION OF JAMES BORROW, M.D.

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I, JAMES BORROW, M.D., declare as follows:

1. I am over 18 and I am making this declaration based on my personal knowledge.

2. I am 77 years old and live in Seattle, Washington with my wife. I was born and raised in Washington State.

3. I received my undergraduate and medical degrees from the University of Washington. After medical school, I interned with the U.S. Public Health Service in San Francisco, served two years as a General Medical Officer with the U.S. Public Health Service, after which I practiced emergency medicine in the San Francisco area. During my work as an emergency department physician, I qualified for, took and passed the board examinations in Family Medicine. In 1983, I returned to Seattle for a residency in diagnostic imaging at the University of Washington. After my residency, I practiced as a general radiologist in Seattle until I retired in 2016.

4. When I retired I was in good health. My wife and I were looking forward to an active retirement, but our lives were disrupted in March 2020 when I was diagnosed with Stage 4 Retroperitoneal Leimyosarcoma. Leimyosarcoma is a rare cancer that starts in smooth muscles that line organs throughout the body, including the stomach, bladder, liver, and arms and legs; in my case the primary tumor is in the pelvis. With disseminated disease in

the liver and lungs, my condition is terminal. When I was first diagnosed, I was told that the median survival is 11-18 months. I am currently receiving chemotherapy treatment for my metastatic disease and my primary pelvic tumor was treated with radiation therapy. Both the radiation therapy and chemotherapy may prolong my life, but are not considered curative. I will soon complete 5 of 6 cycles of my current chemotherapy and will have restaging imaging examinations (PET-CT and routine CT) before completing the 6th cycle of the current regimen. After restaging, my treatment team will give me an updated prognosis.

5. Although I feel that I am managing my mental health related to my terminal diagnosis fairly well, I recognize that it is more trying on a day-to-day basis than I let on. Some days I experience significant anxiety about my condition and how to bring together the threads of my life to make the most of the life I've had and mesh it with the end of my life. At times I feel hammered and overwhelmed by this unexpected diagnosis.

6. So far, I have taken up meditation and have read with great interest various studies, articles, and books related to psilocybin treatment for palliative care patients. I am eager to try this treatment, as I believe it may help me to integrate my terminal diagnosis with what time I have left, so that I can live the rest of my life to the fullest, as well as provide relief from the

anxiety I experience. I do believe that guided psilocybin therapy can be a very useful, integral facet of my care, with the potential of shaping my outlook toward end of life, allowing me to be more comfortable with the process of dying and will facilitate my interactions with those whom I love and care for and who love and care for me. Based on my reading and discussion with friends and family I believe I'll be able to be a more positive, active participant in the end of life process by being involved in psilocybin therapy. While I haven't thought a lot about it, I suspect that if psilocybin therapy is available, I am more likely to avoid assisted suicide and thus prolong my life as an active participant in my care.

7. Recently I volunteered for an approved psilocybin treatment study but I did not meet the criteria to enroll. I have not located an available study for which I meet all of the criteria.

8. I have not found an alternative way to obtain psilocybin treatment. I see a palliative oncologist once a month, and I am hopeful that if this lawsuit is successful, I will be able to work with him or another palliative oncologist to obtain psilocybin treatment.

9. I want to receive this treatment in a legal, comfortable and controlled environment when and where it can be most impactful. That time is right now. I am approaching the median life expectancy for people with my

condition, and while weak and fatigued from my chemotherapy, am comfortable and able to think and communicate clearly. While I hope my treatment team will provide me with new prognosis that gives me significantly more time, I cannot count on it. I need to access to psilocybin in the very near future, in order to receive the most benefit.

I declare under penalty of perjury under the laws of the United States that the foregoing statements are true and correct.

Executed this 18th day of May, 2021, at Seattle, Washington.

James Borrow, MD

JAMES BORROW, M.D.

No. 21-70544

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DECLARATION OF SUSAN PATZ

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I, SUSAN PATZ, declare as follows:

1. I am over 18 and I am making this declaration based on my personal knowledge.

2. I am 62 years old and am a lifelong resident of Washington. I currently live in the town of Monroe with my husband, John. I have two grown children who also live in Washington.

3. In November 2018 I was diagnosed with amyotrophic lateral sclerosis (ALS), known by many as Lou Gehrig's disease. ALS is a disease of the nervous system that causes a progressive loss of muscle control. Over time, people with ALS lose control over the muscles needed to function, including those necessary to walk, speak, eat, and breathe. The disease is fatal and there is no cure. I expect I will live another one-to-two years.

4. When I was first diagnosed with ALS, my main symptom was foot drop—basically, difficulty lifting the front part of my left foot. Since that time, I have lost all muscle control in my left leg and most of the muscle control in my right leg. I can no longer walk or stand. Other parts of my body, including my hands, respiratory muscles, and my swallow are starting to show signs of weakness.

5. Because of the ALS, I have had to give up a lot of the activities I was passionate about. I loved gardening, and I used to delight in driving the tractor

around our property. I loved to swim at the YMCA five days a week. I loved cooking and trying new recipes. I can no longer do any of those things.

6. One of the biggest losses I have had to face is my career. I was a registered nurse for 25 years prior to my diagnosis, primarily in cardiac care. I loved being an RN. It gave me a tremendous sense of purpose and was a big part of my identity. Having to give it up has been extremely difficult for me to cope with.

7. I have dealt with depression at various points throughout my life, but I was always been able to manage it. That changed when I was diagnosed with ALS. Now I live with depression that is constant and severe. I feel like I have been at my rock bottom pretty much continuously for the past two-and-a-half years. I have contemplated suicide more than once.

8. I was always very independent, but as the ALS has progressed I have had to rely on other people more and more. I had to stop driving last summer and lost the ability to walk at around the same time. I am currently able to use a scooter to get around without someone have to push me, but at some point—likely later this year—I will lose that ability as well. As the disease progresses, I will lose the ability to feed myself, bathe myself, use the bathroom on my own, brush my teeth, turn over, and even sit up without assistance. I spend a lot of time thinking about my future. Knowing I will have to rely on others to do even the most basic human tasks makes me feel so demoralized.

9. The person I rely on most is my husband. He has become my main caregiver, and while I am very grateful for his love and support, our roles are changing and this makes me so sad. We used to love travel together around the world. We had planned to travel in our retirement. We used to golf every weekend during the summer. My husband used to call it "The Summer of Golf." We used to be partners. That's all changed. I no longer sleep in the same bed as my husband; I have to sleep in my recliner to keep my head elevated. So much of our relationship is now focused on my disease. And my depression just makes it worse.

10. My motivation level is extremely low—even for activities that used to bring me joy. I used to love to read, and now I struggle to finish a simple article, sometimes reading the same sentence over and over again. My husband and I have chickens and two cats. I used to enjoy interacting with them, but I haven't wanted to do that for a long time. I still have the ability to swallow, but I have no appetite. I used to be a real "foodie." I used to love to plan interesting meals, shop for unusual ingredients, and cook for my family and friends. Now I don't even want to eat. I don't want to have friends over and I don't like to go out in public. I feel like people who look at me now only see a sick person, and I can't bear it.

11. I have a very difficult time falling asleep, even though I take sleep aids. It's not unusual for me to be up until 3:00 or 4:00 in the morning, wanting to fall asleep, but unable to do so.

12. I can't bear to live this way anymore. I want to experience joy during the time I have left. I want to enjoy the company of my family and friends. I want to appreciate my home and my animals. I want to find pleasure in things like reading and food again. I want to stop crying so much.

13. I have tried to treat my depression with therapy and several different medications, but those treatments have provided very little relief. Sertraline, the medication I take now, has been more effective than the others I have tried, but only slightly. And even with this medication, I still suffer the severe and constant depression that I've described, including thoughts of suicide.

14. My husband is a doctor who practices palliative medicine. He has told me about studies involving the use of psilocybin to treat depression. My understanding is that if it is administered in a controlled setting with proper protocols, psilocybin can be very effective in relieving symptoms of depression, particularly in people with a terminal illness. I want to try this treatment. I don't want to keep living in this deep, dark place where my mind has been stuck for the past two-and-a-half years. I don't want to spend the last year or two of my life feeling isolated, depressed, and suicidal. I am desperate to try something that will work, something that will enable me to experience joy and pleasure again. If the Right-to-Try laws don't allow someone like me the chance to try something that may help alleviate my suffering, then what good are they?

I declare under penalty of perjury under the laws of the United States that the foregoing statements are true and correct.

Executed this 11 day of May, 2021, at Monroe, Washington.

Susan Patz

SUSAN PATZ

end of life WASHINGTON
Your life. Your death. Your choice.

PSILOCYBIN THERAPY FOR EMOTIONAL SUFFERING CAUSED BY TERMINAL ILLNESS

POLICY STATEMENT AND REVIEW

Policy Statement

The medical community has made great progress in developing treatments to extend life. It has also created new fields of medicine devoted to treatments for the pain and suffering associated with debilitating or terminal diseases. End of Life Washington (EOLWA) recognizes the evolution of palliative care as an important contributor to the quality of life at its end. This is why we support efforts to legalize the use of psilocybin therapy for depression and anxiety experienced by terminally ill individuals.

Numerous well-controlled, peer-reviewed clinical studies have demonstrated that psilocybin, taken under controlled conditions regarding dosage, setting, and professional guidance, produces significant and enduring positive effects. In addition to reducing anxiety and depression, it also improves death acceptance, life meaning, and optimism, as measured by several valid and reliable tests completed by study subjects.

End of Life Washington advocates for terminally ill individuals to have the right of choice regarding the full range of treatment modalities for their emotional as well as physical care. Psilocybin-assisted psychotherapy is such a modality and should be a legal option, as a part of palliative care, for terminally ill individuals.

Review

1. What is psilocybin?

Psilocybin is a psychoactive substance with mind-altering effects that is found in certain mushrooms, and it has been used for thousands of years to enhance spiritual experiences (https://en.wikipedia.org/wiki/Psilocybin). It acts on serotonin brain receptors, resulting in changes of perception, cognition, and emotion (https://www.heffter.org/#psilocybin). The U.S. government began to study it in the 1950s and 1960s to treat a variety of behavioral health problems, including addiction, PTSD, obsessive-compulsive disorder, treatment-resistant depression, and psychological/existential distress caused by cancer, as well as pain. These early studies were very promising but were not well controlled in light of current clinical research standards. Partly because of the political/cultural climate in the ‘60s and ‘70s and fears raised by recreational use of this and other psychedelic drugs such as LSD, hallucinogenic substances including psilocybin were placed on a “Schedule I” list of drugs

under the Comprehensive Drug Abuse Prevention and Control Act of 1970. This made it illegal to possess, manufacture, or distribute them. However, government-supported, well-designed clinical trials resumed in the 1990s, including with people with a terminal cancer diagnosis who were suffering from existential/psychological distress. Some of the most notable studies have been conducted at Johns Hopkins University and New York University.

This review focuses on the use of psilocybin with terminally ill patients. Psilocybin therapy is of increasing interest to some palliative care specialists as a possible addition to the palliative care toolbox (Byock, 2018; Dyck, 2019). It is also of interest to some advocates for medical aid in dying who wish to improve and expand choices available to terminally ill patients to reduce suffering, enhance quality of life, and die on their own terms.

2. What do the studies show?

Several excellent articles are available that review these studies (see, e.g., Byock, 2018; Griffiths et al., 2016; Nichols et al., 2017; Ross, 2018). They also provide an explanation of the mechanism of psilocybin based on human brain imaging technologies that show how psychedelics temporarily affect brain connectivity networks. This alteration allows for greater cognitive flexibility and creates a temporary disruption of some of the negative and dysfunctional cognitive/emotional patterns people tend to get stuck in that are part of normal consciousness and in particular cause rumination, anxiety, and depressive thinking ("the default mode network" [Pollan, 2018]) and may explain why psilocybin seems to be effective for such a broad range of psychological symptoms.

Recent studies report several interesting and consistent findings. A terminal cancer diagnosis is well-known to produce anxiety and depression (including suicidal ideation) in a significant number of individuals, so most of the studies involving people with terminal illness have studied cancer-related psychiatric distress. First, psilocybin therapy, when properly administered under controlled, supervised, supportive conditions, produces no serious psychiatric or medical adverse events. (There may be some initial anxiety or nausea, but this subsides and has no lasting negative impact.) Second, in a very significant number of subjects it produces immediate meaningful and enduring reductions in psychiatric and existential distress, as well as improvements in quality of life, death acceptance, life meaning, optimism, and spiritual meaning, as measured by several valid and reliable standardized tests completed by the individual and also validated by people who know the individual well enough to observe effects. Third, two-thirds or more of subjects rated the experience as being one of the most personally meaningful or spiritually significant events in their lives.

Some studies involved several sessions of therapy, but a significant number used only one session with a single dose of psilocybin. Sessions are highly controlled to ensure that attention is paid to what are considered the three most important factors for a positive experience: substance (the drug is obtained from an approved manufacturer with standardized dosages), set (clear expectations, arrived at through preparation and information about the experience beforehand), and setting (safe, comfortable, and with trained guides). Preliminary screening for any contraindications related to medications, medical conditions, or serious psychiatric conditions is also essential. This is in great contrast with self-directed recreational use, which often involves a drug from an unknown source with uncertain dosage and no trained guide. In addition to following rigorous design models to ensure reliable and

valid data, several protocols are now standard in studies of "psilocybin-assisted psychotherapy" with individuals with terminal illness:

- Controlled randomized study design.
- Exclusion of individuals with major psychiatric illness.
- Careful preparation and instructions for the session conducted by trained therapists.
- Standardized dosage from known psilocybin manufacturer.
- Dosing session conducted in a comfortable living-room type setting providing safety and comfort with two trained therapists as guides.
- One 6-8 hour session.
- Post-session integration experience to debrief, with the same guides.
- Six month follow up.

A fascinating and informative book on this topic was written by Michael Pollan (2018), a highly respected journalist on topics like food, nature, and science who is by no means a true believer. Pollan started out as a skeptic but researched the literature very thoroughly, which he presents in a clear and objective manner. He ended up having his own psychedelic experience and describes it.

Byock (2018) is a prominent palliative care expert who argues that in addition to alleviating physical distress, palliative care should also address the suffering caused by emotional, social, existential, and spiritual distress at the end of life. He supports psychedelic therapy and argues that it is a right-to-try issue.* Byock is a long-standing opponent of medical aid in dying, but he suggests that it might be possible to build consensus for reclassifying psilocybin from being an illegal Schedule 1 drug among typically disparate groups: conservatives, progressives, and both opponents and supporters of legalized medical aid in dying. His hope is that some terminally ill people interested in DWD (Death With Dignity) might decide not to pursue this option after receiving psilocybin therapy. This is debatable as DWD supporters argue that a desire for DWD is not the same as suicidality (which is caused by psychiatric symptomatology) but is based on existential and quality-of-life concerns related to terminal illness. Annual DWD reports from Oregon and Washington show that the most consistently reported reasons people give when requesting DWD are existential, the top reason being loss of autonomy (85%), not about physical suffering or psychiatric symptomatology (see e.g., https://www.doh.wa.gov/Portals/1/Documents/Pubs/422-109-DeathWithDignityAct2018.pdf). There is some anecdotal evidence regarding ketamine, a legal psychedelic sometimes used with terminally ill patients, that "whereas some…have postponed their option for MAID [medical aid in dying], others have embraced it" https://www.medscape.com/viewarticle/924261. Whether and how psilocybin therapy might affect the desire for DWD by either increasing it or decreasing it would be interesting to study.

3. Summary

Studies show that psilocybin therapy is effective in relieving emotional and existential distress at the end of life for 65-85% of terminally ill people in clinical trials, when it's administered properly. There are no lasting negative effects and many significant and enduring positive benefits. These findings fit in with the goals of palliative care, which "Integrates the psychological and spiritual aspects of patient care; enhance[s] quality of life…" (https://www.who.int/cancer/palliative/definition/en/). The limitation is that it not be misused – protocols need to be followed that include screening; a reputable drug at the right dosage; a safe place for the experience; the presence of trained guides; and preparation, administration, and integration by those guides.

The Heffter Research Institute, which promotes scientific research with psychedelics "in order to contribute to a greater understanding of the mind leading to the improvement of the human condition, and to alleviate suffering" (https://www.heffter.org/#psilocybin), cautions the following:

> Psilocybin is a powerful medicine and it is Heffter's position that the positive effects found in research to date are achieved only when prescribed by a doctor and used in a therapeutic setting. Safety has not been demonstrated for psilocybin when used outside of a structured clinical or laboratory setting and we strongly caution against recreational use of psilocybin because of potential adverse psychological reactions.

It seems very possible that psilocybin therapy will eventually become an accepted palliative care tool by many scientific, palliative care, and hospice communities. Organizations supporting medical aid in dying need to consider at least two positions regarding the possible support and legalization of psilocybin therapy. One position is that psilocybin therapy belongs in the palliative/hospice care domain and lies outside the scope of organizations that steward medical aid in dying, specifically DWD laws. Another position is to view it as one of the choices terminally ill people should have, which include how to die, as well as ways to ease suffering related to dying (Tucker, 2020).

4. End of Life Washington

EOLWA has adopted the second position outlined above. On September 18, 2020, the Board of Directors approved a policy supporting psilocybin-assisted psychotherapy as a legal option, as a part of palliative care for terminally ill patients.

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*The Right to Try Act is a law that allows "patients who have tried all approved treatment options and who are unable to participate in a clinical trial to access certain unapproved treatments." There are several stipulations and requirements that need to be met. Currently 41 states including Oregon and Washington have RTT laws (http://righttotry.org/about-right-to-try/). Also see Tucker (2020).

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Tucker, K.L. (2020). Oregon's pioneering effort to enact state law to allow access to psilocybin, a new palliative care tool for patients suffering anxiety and depression. *Willamette Law Review* (in press).

Additional Resources

The Heffter Research Institute https://www.heffter.org/

The Johns Hopkins Center for Psychedelic and Consciousness Research http://hopkinspsychedelic.org

TheraPsil (Canada) https://therapsil.ca

Report Prepared by Judith R Gordon PhD
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Special Report

Taking Psychedelics Seriously

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Abstract

Background: Psychiatric research in the 1950s and 1960s showed potential for psychedelic medications to markedly alleviate depression and suffering associated with terminal illness. More recent published studies have demonstrated the safety and efficacy of psilocybin, MDMA, and ketamine when administered in a medically supervised and monitored approach. A single or brief series of sessions often results in substantial and sustained improvement among people with treatment-resistant depression and anxiety, including those with serious medical conditions.
Need and Clinical Considerations: Palliative care clinicians occasionally encounter patients with emotional, existential, or spiritual suffering, which persists despite optimal existing treatments. Such suffering may rob people of a sense that life is worth living. Data from Oregon show that most terminally people who obtain prescriptions to intentionally end their lives are motivated by non-physical suffering. This paper overviews the history of this class of drugs and their therapeutic potential. Clinical cautions, adverse reactions, and important steps related to safe administration of psychedelics are presented, emphasizing careful patient screening, preparation, setting and supervision.
Conclusion: Even with an expanding evidence base confirming safety and benefits, political, regulatory, and industry issues impose challenges to the legitimate use of psychedelics. The federal expanded access program and right-to-try laws in multiple states provide precendents for giving terminally ill patients access to medications that have not yet earned FDA approval. Given the prevalence of persistent suffering and growing acceptance of physician-hastened death as a medical response, it is time to revisit the legitimate therapeutic use of psychedelics.

Keywords: depression; existential suffering; MDMA; palliative care patients; pharmaco-assisted therapy; post-traumatic stress disorder; psilocybin; psychedelic drugs; therapeutic use

Recently published studies in peer-reviewed journals[1–4] and high-profile articles in the *New Yorker*,[5] *New York Times*,[6] and *Wall Street Journal*,[7] have rekindled professional and public interest in the therapeutic use of psychedelic drugs. It is easy to understand the enthusiasm. The magazine and newspaper articles include accounts of patients with profound depression, demoralization associated with terminal illness, and anxiety related to post-traumatic stress disorder (PTSD), who experienced remarkable improvements, including some who had previously considered suicide.

Nevertheless, psychiatric and palliative care clinicians who care for profoundly depressed, anxious, and seriously ill patients have every reason to be skeptical. As people become more mentally or physically ill and established treatments remain insufficiently effective, patients' susceptibility increases. Physicians play an important role in protecting vulnerable patients from spurious, nonevidence-based miracle cures, as well as from scientifically grounded, but overly zealous burdensome treatments that are certain to do more harm than good.

An abundance of caution should be accorded psychedelics, which carry real risks and are formally designated Schedule I drugs, signifying that they are dangerous, without therapeutic value, and illegal. Older clinicians remember news stories of deaths of individuals high on hallucinogens who thought they could fly, those with bad trips and flashbacks, and studies that purported to show chromosome damage associated with use of lysergic acid diethylamide (LSD).

However, given the extent of persistent emotional and existential suffering that palliative care clinicians encounter in the patients we serve, these medications deserve serious consideration by our field.

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Background

Psychedelic properties of specific plants (mushrooms and cactuses) have been used for centuries by indigenous cultures to induce expanded states of consciousness and spiritual experiences.[8–10] During the 1950s and early 1960s, research sponsored by the National Institute of Mental Health demonstrated potential for drugs of this class to markedly alleviate depression and existential suffering among people with cancer.[11–13] Subsequently, nonmedical use of these drugs and associated political and cultural upheavals resulted in the Schedule I classification, abruptly banning psychedelics from further clinical research and medical use. Although many of the mid-twentieth century clinical trials involved people with terminal conditions, few references to these published studies can be found in the literature of palliative medicine, a young specialty that developed after this period. Over the past 20 years, a few small clinical studies were conducted abroad, mostly in Europe and the United Kingdom. In the United States, over the past decade, with support from the Multidisciplinary Association for Psychedelic Studies and private funders, a few tenacious researchers earned governmental permission to carry out carefully designed trials of pharmacoassisted therapy with psilocybin and 3,4-Methylenedioxymethamphetamine (MDMA), more commonly known by its street names, Ecstasy and Molly.

The recently published research strengthens findings of earlier studies, showing significant efficacy and few adverse effects when these medications are administered as adjuncts to psychotherapy to carefully screened patients, under medical supervision.[1–3] Three drugs, psilocybin, ketamine, and MDMA, have attracted most of the recent attention. Psilocybin, a naturally occurring drug found in psilocybe mushrooms, has strong and durable benefits for some patients with treatment-resistant depression, and for those with demoralization, anxiety, and depression associated with terminal illness. Ketamine, a Federal Drug Administration (FDA)-approved anesthetic with analgesic and psychedelic properties, has been used off-label in patients with treatment-resistant depression. In case studies and small clinical series, ketamine has shown notably positive effects.[14–16] MDMA, a drug synthesized in 1912 as a potential anticoagulant, was later found to have strong psychoactive properties. In the 1970s and early 1980s, psychiatrists who administered MDMA in the context of psychotherapy observed sometimes dramatic improvements in patients suffering from severe, treatment-resistant PTSD.[17,18]

In deciding how to think about these drugs, the distinction between skepticism and cynicism bears examining. Skepticism is warranted, but cynical nonscientific bias can result in therapeutic nihilism. The history of medicine is studded with occasional leaps in progress consider small pox vaccination, penicillin, and computed tomography scans that, shortly before they occurred, might have seemed too good to be true. When I graduated from medical school, the idea that duodenal ulcers were caused by bacteria would have been risible; stem cell transplants and gene-editing therapies were the stuff of science fiction. Surprising medical advances humbly remind us to suspend cynicism and that honest inquiry is warranted.

The Need Is Great

While not only for people who are dying, specialty palliative care teams serve the sickest patients in our health systems and communities. It is, therefore, not surprising that we occasionally encounter incurably ill people whose suffering persists despite all available evidence-based treatments.

In treating pain and other physical distress, established treatment protocols guide escalations of doses and combinations of analgesics and co-analgesic medications. When a patient is dying and physical pain, dyspnea, seizures, or agitated delirium persists and causes intolerable suffering, as a last resort, comfort can reliably be achieved with proportionate sedation.[19]

However, not all suffering is based solely in physical distress. Palliative care clinicians and teams also encounter patients whose misery is rooted in emotional, social, existential, or spiritual distress. Cancer, heart failure, liver failure, and amyotrophic lateral sclerosis (ALS) or motor neuron disease are among the diseases that can result in a progression of personal losses: Of feeling in control. Of taking care of one's self. Of contributing to others. Of enjoyment. Of meaning and purpose. Ultimately, some ill people say they have lost any reason to go on living.

People who are incurably ill and living with progressive disease-related disabilities can experience anxiety, depression, and demoralization.[20,21] Psychotherapy alone and drug treatments for such syndromes are often insufficient. Medications for depression may take weeks to become effective or prove ineffective. Antidepressants and anxiolytics carry side effects that can include mental slowing and confusion. These adverse effects are particularly common and hazardous in patients with advanced physical illness, who are also at risk of polypharmacy, multidrug interactions, and concomitant disequilibrium and falls. When nonphysical suffering persists despite prudent approaches, published, evidence-based guidelines are limited.

Severe psychological and existential suffering can rob people of feeling that life is worth living. A sense of unending helplessness and hopelessness compels some to consider ending their lives. Suicide rates have risen 24% over the past two decades and are highest among middle-aged and elderly adults, particularly men who may suffer most from feelings of dependency.[22,23] Public health data from Oregon show that since implementation of the Death with Dignity Act, the large majority of patients who received prescriptions for lethal drugs were motivated by nonphysical suffering. Current or fear of future pain contributed in just 26.4% of cases, while loss of autonomy (91.4%), decreased ability to enjoy life (89.7%), and loss of dignity (77.0%) most often brought these people to contemplate hastening their deaths.[24]

Exercising Abundance of Caution: Screening, Supervision, Set and Setting

Prescribed to carefully screened patients, in recommended doses, in the context of professional counseling and supervision, psilocybin and MDMA have proven to be notably safe. They have no tissue toxicity, do not interfere with liver function, have scant drug drug interactions, and carry no long-term physical effects.

These drugs are not intoxicants in the usual sense. They do not dull the senses or induce sleepiness. On the contrary, sensory perception is intensified and attention is aroused. Although abuse syndromes have been reported, few people become habituated to these drugs.

Adverse physiological effects are few and of short duration, but can be substantial. During the onset of psychedelic

experiences nausea and vomiting are not unusual. In this first hour or more, visual and spatial orientation are commonly disrupted, which can give rise to anxiety. Sympathetic nervous system arousal may occur both because of fear, and from direct effects of the drugs. Particularly during the initial phase of sessions, psychedelics dissolve barriers between physical senses resulting in synesthesia; touches, smells, and tastes can take on sounds, shapes and colors. Similarly, emotions and thoughts may evoke visual images and sounds. These phenomena explain why the term hallucinogen is often used synonymously with psychedelics to refer to this class of drugs.

Clinicians and researchers familiar with this class of pharmaceuticals emphasize the importance of screening, supervision, and ''set and setting.''

Screening

Not every suffering patient is a candidate for therapy involving psychedelic drugs. As a general guideline, people who have cognitive and emotional conditions associated with disorganized or diminished ego strength are not good candidates for pharmaco-assisted therapy with psychedelics. MDMA may represent a partial exception to this exclusion, because it has fewer cognitive and sensory effects and more salutary emotional and interpersonal properties. Contraindications include people with borderline personality disorders or schizophrenic tendencies.

Supervision

Supervision is necessary for ensuring safety of psychedelic experiences. Short-term psychological effects are profound. If used in unsupervised fashion by unselected and unprepared people, these drugs can be highly dangerous and, in extreme cases, cause death. The sensory effects described above interfere with hand-eye coordination and fine motor function, making operating a vehicle or machinery or even walking in public potentially dangerous. These effects are sufficient to emphasize that professionals who are skilled in managing adverse effects must be present. Most research into pharmaco-assisted therapy with psychedelics has by protocol required subjects to remain in a single comfortable room throughout the sessions. In addition to safety, the supervising therapists are able to guide patients through their experiences to optimize the drug's beneficial potential.

Set and setting

Anthropologists studying traditional use of psychedelics by shamans and indigenous people recognized the influence of expectations and motivation on subjective experience. Since the earliest psychological research into pharmaco-assisted therapy with psychedelics, clinicians have emphasized the importance of ''set and setting.''

The dissolution of assumptions and diminution of barriers caused by these drugs extend to psychological and interpersonal realms of experience. An enhanced sense of connection to others not only underpins some of the therapeutic effects, but also results in vulnerability to emotional contagion. When taken without adequate preparation and when surroundings are anxiety-provoking either physically uncomfortable or emotionally intimidating the psychedelic experience predictably results in fear, a prolonged sense of dread, or full panic. Conversely, in controlled settings with elements of soft light, art, and appropriate music, or nature, and gentle, compassionate people, such adverse reactions are rare.

With adequate counseling and preparation, and when psychedelic experiences unfold in calm, aesthetically pleasing environments, they prove beneficial in a high proportion of cases.[17] In these situations, the healing motivations of both therapists and patients may contribute to therapeutic outcomes.

Therapeutic Effects

Clinical case studies and research trials describe common patterns of subjective experiences that are associated with therapeutic benefits for people with severe anxiety and depression. As the initial phase of psychedelic experience wanes and people regain familiar barriers between visual, auditory, tactile, olfactory senses, people typically report heightened cognitive clarity and expanded emotional receptivity. Previously unrecognized or unquestioned assumptions related to one's place in the world and relationships to nature, one's physical and social environments become available to being considered anew.

While psychedelic experiences vary significantly from one individual to another, research subjects and people interviewed for journalistic articles commonly express attributes, which include heightened clarity and confidence about their personal values and priorities, and a renewed or enhanced recognition of intrinsic meaning and value of life. People often voice a sense of exhilaration, insight, and strengthened connection to others, as well as a richer sense of relationship with nature or God.[25] People who take psychedelics with an intention of spiritual introspection often report that the drugs opened windows into deeper realms of existential experience.[5,9] In safe and supportive environments, these effects typically induce a state of wonder, conceptual frame shift, expanded capacity for love, and an intensified sense of connection. Patients living with medical conditions that had robbed them of hope or reason to live may experience a transformative shift in perspective and experience of inherent meaning, value, and worth.

Not all psychedelics drugs are alike and subcategories have been described.[10] Drugs, such as psilocybin and LSD, classified as entheogens,[26] are associated with introspection and new insights, shifts of perspective, and reframing of experience and relationship to others and the world. MDMA is characterized as an empathogen, referring to prominent emotional effects of interpersonal warmth, empathy, and openness.[27] These properties may underlie the benefits of MDMA in the context of therapy for those suffering from severe PTSD.

For most of these drugs, a single six to eight-hour session or short series of sessions suffices for therapeutic benefit. Alleviation of anxiety and depression may persist for weeks to months and, for some, proves permanent. Exceptions to this treatment pattern include protocols of daily low-dose ketamine for depression[15] and recent nonmedical reports of daily or every third day micro-dosing of LSD.[28,29]

Political and Regulatory Considerations

Psychedelic drugs were closely associated with the cultural wars of the 1960s and 1970s when strong political undercurrents contributed to this class of drugs being classified Schedule I. Similarly, MDMA became well known as Ecstasy or Molly, a popular, illicit rave and party drug.[7] In the

mid-1980s, despite evidence of MDMA's striking efficacy and relative safety when used therapeutically, the FDA declared MDMA a Schedule I agent. Court rulings challenged that classification; however, in 1998 the FDA reaffirmed and made the Schedule I classification permanent.[30]

The process of renewing clinical research of psychedelics has been long and painstaking. Future efforts to reclassify selected psychedelics, such as psilocybin, as Schedule II drugs, enabling both research and clinical administration will likely meet predictable political resistance. There are compelling reasons, however, to address the expected concerns of opponents and proceed with efforts to reclassify these drugs.

Treatment-resistant depression and anxiety associated with PTSD causes untold suffering and contributes to thousands of deaths each year. A few population health studies suggest that rising suicide rates may in part be due to suicide becoming less shameful and more socially acceptable, lowering barriers for people who feel hopeless.[31,32] A person with severe depression, who has a coexisting serious, life-threatening physical condition, may feel that his or her quality of life is not worth living and may forgo arduous, but potentially life-saving treatments. Additionally, nearly one sixth of Americans live in states where physician-hastened death is legal and those with terminal illness may choose this option in absence of alternative sources of relief.

There may be higher ground on which political conservatives and progressives as well as those on opposing sides of the issue of legalizing physician-hastened death might build consensus. Given the life-threatening nature of persistent, treatment-resistant depression and PTSD, including among veterans of America's wars, and the rising incidence of suicide, the reclassification of psilocybin and MDMA can be legitimately cast as a right-to-try issue. Right-to-try legislation has been used to provide terminally ill patients access to potentially life-extending medications that have been tested in Phase I trials but are of uncertain benefit.[33,34] Similarly, the FDA's expanded access or compassionate use provisions may make use of drugs that have not been approved available to patients who are otherwise facing death.[35,36] By diminishing a desire to die among people with severe depression, anxiety, PTSD, and those with terminal cancers, genetic and neurodegenerative diseases, psychedelics may have greater life-saving effects than other drugs that have earned right-to-try and expanded access status.[37]

Business Considerations

Business models for medical uses of these drugs are not clearly defined. Alleviating persistent depression or PTSD with one or two doses of an inexpensive, un-patentable compound may threaten existing markets for antidepressant and anxiolytic medications. Therefore, it is possible that the pharmaceutical industry may oppose legalization and supervised use of these medications. If so, industry lobbying could complicate regulatory processes needed to research legitimate uses of these drugs.

The way forward may include folding the cost of these medications into professional fees for pharmaco-assisted therapy.[38] This alternative business model would align well with the therapeutic rationale for requiring psychedelic sessions to be supervised by trained counselors, who are able to control set and setting and capable of preventing and managing any adverse reactions.

Final Thoughts

Faced with novel therapies with reported clinical benefits that seem too good to be true, skepticism is warranted to protect vulnerable patients from harm. Cynicism, however, may prove more dangerous still. Unscientific bias and nihilistic assumptions can keep effective treatments from people who desperately need them.

Despite the controversial history of psychedelic medications, palliative specialists who care for patients with serious medical conditions and common, difficult-to-treat nonphysical suffering have a duty to explore these hopeful, potentially life-preserving treatments. Against the backdrop of physician-hastened death becoming legal in five states, expanded research of clinical psychedelics must proceed.

In reexamining the use of psychedelics in pharmaco-assisted therapy, we must not allow preconceptions, politics, or puritanism to prevent suffering people, who are now considered helpless and hopeless, from receiving promising, at times life-saving, treatments.

Author Disclosure Statement

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FDA FACT SHEET

Right to Try

What is Right to Try?

- Right to Try is one pathway for patients diagnosed with life-threatening diseases or conditions who have exhausted all approved treatment options and are unable to participate in a clinical trial to access certain drugs that have not been approved by the Food and Drug Administration (FDA).
- Right to Try allows eligible patients to request access to certain investigational drugs (including biologics[1]) that have not yet been approved by the FDA.
- Under Right to Try, patients and their doctors work with a company that is developing a drug or biologic to request access without involving FDA in the process.
- The FDA does not review or approve Right to Try requests.

How do I know if I am eligible to request access to a drug or biologic under Right to Try?

Patients who are eligible under the Right to Try Act[2] meet the following criteria:

- You have a life-threatening disease or condition.
- You have exhausted approved treatment options and are unable to participate in a clinical trial involving the drug or biologic, as certified by your doctor.
- You (or your legally authorized representative) have given written informed consent to the doctor regarding the investigational drug.

How do I know if a drug or biologic is available under Right to Try?

- The Right to Try Act sets forth specific criteria for a drug or biologic to be eligible for this pathway, such as a drug or biologic being under clinical trial investigation.
- The Right to Try Act does not require a manufacturer or sponsor to provide access to drugs or biologics. Further, FDA cannot require a manufacturer or sponsor to provide access to drugs or biologics under the Right to Try Act.

[1]A biologic is a product that is made from a living thing or its products. Some examples include vaccines, allergy shots, blood, genes, tissues and cells.
[2] The Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017.

- Talk to your doctor. You or your doctor can then consult with the manufacturer or sponsor to request access for the drug or biologic.
- Manufacturers or sponsors may provide information about whether their drug or biologic is eligible under the Right to Try Act and whether they are willing to make their drugs or biologics available to patients who qualify to request access under the Right to Try Act.

What else do I need to know about Right to Try?

- Through the Investigational New Drug (IND) application process, the FDA typically reviews the safety of each proposed use of an investigational new drug before it can be provided to patients. While the Right to Try Act requires drugs to meet specific criteria in order to be eligible to be provided to patients under the Right to Try pathway, drugs that are provided through the Right to Try pathway are generally exempt from these IND reviews.
- Drugs and biologics available under Right to Try have not been approved by the FDA. This means that:
    - *Safety*: The FDA has not determined whether drugs and biologics made available under Right to Try are safe and if there could be serious risks or side effects.
    - *Effectiveness*: The FDA has not determined whether drugs and biologics made available under Right to Try can lead to any improvement in disease or symptoms.
- Discuss the potential benefits and risks of receiving drugs through Right to Try with your doctor.

For more information:

- **Right to Try:** https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try
- **Clinical Trials:** https://www.fda.gov/patients/clinical-trials-what-patients-need-know
- **FDA's Drug Review Process:** https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective

Have you seen our Blog? FDA Voice

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, and products that give off electronic radiation, and for regulating tobacco products.

FINAL BILL REPORT
SSB 5035

C 212 L 17
Synopsis as Enacted

Brief Description: Concerning patients' access to investigational medical products.

Sponsors: Senate Committee on Health Care (originally sponsored by Senators Pedersen, Rivers, Cleveland, Becker, Keiser, Walsh, Conway, Bailey, O'Ban, Mullet, Kuderer, Darneille and Wellman).

Senate Committee on Health Care
House Committee on Health Care & Wellness
House Committee on Appropriations

Background: The United States Food and Drug Administration (FDA) enforces the federal regulatory pathway for approval of medical therapies, including drugs. Until the FDA approves the drug for medical use, the drug may not be sold or distributed. Drugs typically undergo multiple phases of clinical trials to establish the drug's safety and efficacy. In Phase I, researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects. Phase I clinical trials may last several months to a year. Phases II and III involve larger groups of people to further evaluate its safety, confirm its effectiveness, and collect new information to allow the drug to be used safely. Phases II and III may each take two or more years to complete.

If individuals do not qualify for a clinical trial but may benefit from treatment with an investigational drug, the FDA has an expanded access pathway that permits access to these drugs if: the individual has a serious or immediately life-threatening condition and there is no satisfactory alternative therapy, the potential benefit outweighs the treatment risks, and providing the investigational drug will not interfere with the clinical trial's process or compromise the product's development.

Right to try laws enable terminally ill patients to access experimental drugs, biologics, and devices that are still in a research phase and have not yet been approved for use by the FDA. In general, right to try laws permit patient access to an investigational drug if: the patient is terminally ill, a physician recommends use of the treatment, the patient provides informed consent, and the treatment has completed a Phase 1 clinical safety/dose limitation trial. They do not require that the patient be in a clinical trial or be otherwise approved by the FDA to use the drug.

This analysis was prepared by non-partisan legislative staff for the use of legislative members in their deliberations. This analysis is not a part of the legislation nor does it constitute a statement of legislative intent.

Summary: Patients who are suffering from a serious or immediately life-threatening disease or condition may request a pharmaceutical manufacturer to make an investigational product available to the patient. In order to qualify for an investigational product, the patient must be at least 18 years old and be a Washington resident. The patient's treating physician must recommend treatment with the investigational product after informing the patient of FDA-approved treatment options. Finally, the patient must provide written, informed consent for the use of the investigational product.

Written, informed consent must include the following:

- an assertion that the patient has a serious or immediately life-threatening disease and currently approved treatments are unlikely to prolong the patient's life;
- potentially best and worst outcomes of the investigational product;
- a statement that the patient's health benefit plan is not obligated to pay for the investigational product or harm caused to the patient by the product; and
- that the patient is liable for all expenses consequent to the use of the investigational product.

The eligible patient and their treating physician may request that a drug manufacturer make an investigational product available for treatment of the patient. The manufacturer may, but is not required to, make the product available to the patient.

Health carriers may, but are not required to, provide coverage for the cost or the administration of an investigational product. The health carrier may deny coverage to an eligible patient who is treated with an investigational product from harm caused by the treatment. The health carrier is not required to cover costs associated with receiving the investigational product or costs associated with an adverse effect resulting from the product. The health carrier may not deny coverage for: the eligible patient's serious or immediately life-threatening disease or condition, benefits that accrued before the day on which the patient was treated with the investigational product, or palliative care for a patient who ceases treatment of the investigational product.

It is not an act of professional misconduct for a health care practitioner to recommend or administer an investigational product to an eligible patient.

Unless gross negligence or willful or wanton misconduct occurs, immunity from civil or criminal liability and administrative actions are provided to:

- health care practitioners who treat a patient with an investigational product;
- health care practitioners who recommend or request an investigational product or refuse to recommend or request an investigational product;
- manufacturers that provide investigational products to a health care practitioner;
- health care facilities where an investigational product is administered or provided to a patient; and
- health care facilities that do not allow health care providers to provide treatment with an investigational product or enforces a policy it has adopted regarding treatment with investigational products.

Votes on Final Passage:

Senate	49	0	
House	97	0	(House amended)
Senate	48	0	(Senate concurred)

Effective: July 23, 2017

Original Paper

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

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Abstract

Cancer patients often develop chronic, clinically significant symptoms of depression and anxiety. Previous studies suggest that psilocybin may decrease depression and anxiety in cancer patients. The effects of psilocybin were studied in 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. This randomized, double-blind, cross-over trial investigated the effects of a very low (placebo-like) dose (1 or 3 mg/70 kg) vs. a high dose (22 or 30 mg/70 kg) of psilocybin administered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up. Instructions to participants and staff minimized expectancy effects. Participants, staff, and community observers rated participant moods, attitudes, and behaviors throughout the study. High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. 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. Participants attributed improvements in attitudes about life/self, mood, relationships, and spirituality to the high-dose experience, with >80% endorsing moderately or greater increased well-being/life satisfaction. Community observer ratings showed corresponding changes. Mystical-type psilocybin experience on session day mediated the effect of psilocybin dose on therapeutic outcomes.

Trial Registration
ClinicalTrials.gov identifier: NCT00465595

Keywords
Psilocybin, hallucinogen, cancer, anxiety, depression, symptom remission, mystical experience

Introduction

Cancer patients often develop a chronic, clinically significant syndrome of psychosocial distress having depressed mood, anxiety, and reduced quality of life as core features, with up to 40% of cancer patients meeting criteria for a mood disorder (Holland et al., 2013; Mitchell et al., 2011). In cancer patients, depression and anxiety have been associated with decreased treatment adherence (Arrieta et al., 2013; Colleoni et al., 2000), prolonged hospitalization (Prieto et al., 2002), decreased quality of life (Arrieta et al., 2013; Skarstein et al., 2000), and increased suicidality (Shim and Park, 2012). Depression is an independent risk factor of early death in cancer patients (Arrieta et al., 2013; Pinquart and Duberstein, 2010). Antidepressants and, less frequently, benzodiazepines are used to treat depressed mood and anxiety in cancer patients, although evidence suggesting efficacy is limited and conflicting, and benzodiazepines are generally only recommended for short-term use because of side effects and withdrawal (Grassi et al., 2014; Ostuzzi et al., 2015; Walker et al., 2014). Although psychological approaches have shown only small to medium effects in treating emotional distress and quality of life, with low quality of reporting in many trials (Faller et al., 2013), there are several promising interventions utilizing existential orientations to psychotherapy (Breitbart et al., 2015; Spiegel, 2015).

The classic hallucinogens, which include psilocybin (psilocin) and (+)-lysergic acid diethylamide (LSD), are a structurally diverse group of compounds that are 5-HT_{2A} receptor agonists and produce a unique profile of changes in thoughts, perceptions, and emotions (Halberstadt, 2015; Nichols, 2016). Several unblinded studies in the 1960s and 70s suggested that such compounds might be effective in treating psychological distress in cancer patients (Grof et al., 1973; Kast, 1967; Richards et al., 1977); however, these studies did not include the comparison conditions that would be expected of modern psychopharmacology trials.

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Subsequently, human research with these compounds was halted for almost three decades because of safety and other concerns raised in response to widespread non-medical use in the 1960s. Recent resumption of clinical research with these compounds has established conditions for safe administration (Johnson et al., 2008; Studerus et al., 2011).

Two recent double-blind, placebo-controlled studies with the classic hallucinogens psilocybin (Grob et al., 2011) and LSD (Gasser et al., 2014) examined effects in 12 patients with life-threatening illness, including cancer. Both studies showed promising trends toward decreased psychological distress. Of most relevance to the present study with psilocybin, Grob and colleagues showed that a low-moderate dose of psilocybin (14 mg/70 kg) decreased a measure of trait anxiety at 1 and 3 months and depressed mood at 6-month follow-up. Also relevant, a recent open-label pilot study in 12 patients with treatment-resistant depression showed marked reductions in depressive symptoms 1 week and 3 months after administration of 10 and 25 mg of psilocybin in two sessions separated by 7 days (Carhart-Harris et al., 2016).

The present study provides the most rigorous evaluation to date of the efficacy of a classic hallucinogen for treatment of depressed mood and anxiety in psychologically distressed cancer patients. The study evaluated a range of clinically relevant measures using a double-blind cross-over design to compare a very low psilocybin dose (intended as a placebo) to a moderately high psilocybin dose in 51 patients under conditions that minimized expectancy effects.

Methods

Study participants

Participants with a potentially life-threatening cancer diagnosis and a DSM-IV diagnosis that included anxiety and/or mood symptoms were recruited through flyers, internet, and physician referral. Of 566 individuals who were screened by telephone, 56 were randomized. Figure 1 shows a CONSORT flow diagram. Table 1 shows demographics for the 51 participants who completed at least one session. The two randomized groups did not significantly differ demographically. All 51 participants had a potentially life-threatening cancer diagnosis, with 65% having recurrent or metastatic disease. Types of cancer included breast (13 participants), upper aerodigestive (7), gastrointestinal (4), genitourinary (18), hematologic malignancies (8), other (1). All had a DSM-IV diagnosis: chronic adjustment disorder with anxiety (11 participants), chronic adjustment disorder with mixed anxiety and depressed mood (11), dysthymic disorder (5), generalized anxiety disorder (GAD) (5), major depressive disorder (MDD) (14), or a dual diagnosis of GAD and MDD (4), or GAD and dysthymic disorder (1). Detailed inclusion/exclusion criteria are in the online Supplementary material. The Johns Hopkins IRB approved the study. Written informed consent was obtained from participants.

Study design and overview

A two-session, double-blind cross-over design compared the effects of a low versus high psilocybin dose on measures of depressed mood, anxiety, and quality of life, as well as measures of short-term and enduring changes in attitudes and behavior. Participants were randomly assigned to one of two groups. The Low-Dose-1st Group received the low dose of psilocybin on the first session and the high dose on the second session, whereas the High-Dose-1st Group received the high dose on the first session and the low dose on the second session. The duration of each participant's participation was approximately 9 months (mean 275 days). Psilocybin session 1 occurred, on average, approximately 1 month after study enrollment (mean 28 days), with session 2 occurring approximately 5 weeks later (mean 38 days). Data assessments occurred: (1) immediately after study enrollment (Baseline assessment); (2) on both session days (during and at the end of the session); (3) approximately 5 weeks (mean 37 days) after each session (Post-session 1 and Post-session 2 assessments); (4) approximately 6 months (mean 211 days) after Session 2 (6-month follow-up).

Interventions

Meetings with session monitors. After study enrollment and assessment of baseline measures, and before the first psilocybin session, each participant met with the two session monitors (staff who would be present during session days) on two or more occasions (mean of 3.0 occasions for a mean total of 7.9 hours). The day after each psilocybin session participants met with the session monitors (mean 1.2 hours). Participants met with monitors on two or more occasions between the first and second psilocybin session (mean of 2.7 occasions for a mean total of 3.4 hours) and on two or more occasions between the second session and 6-month follow-up (mean of 2.5 occasions for a mean total of 2.4 hours). Preparation meetings, the first meeting following each session, and the last meeting before the second session were always in person. For the 37 participants (73%) who did not reside within commuting distance of the research facility, 49% of the Post-session 1 meetings with monitors occurred via telephone or video calls.

A description of session monitor roles and the content and rationale for meetings between participants and monitors is provided elsewhere (Johnson et al., 2008). Briefly, preparation meetings before the first session, which included discussion of meaningful aspects of the participant's life, served to establish rapport and prepare the participant for the psilocybin sessions. During sessions, monitors were nondirective and supportive, and they encouraged participants to "trust, let go and be open" to the experience. Meetings after sessions generally focused on novel thoughts and feelings that arose during sessions. Session monitors were study staff originally trained by William Richards PhD, a clinical psychologist with extensive experience conducting studies with classic hallucinogens. Monitor education varied from college graduate to PhD. Formal clinical training varied from none to clinical psychologist. Monitors were selected as having significant human relations skills and self-described experience with altered states of consciousness induced by means such as meditation, yogic breathing, or relaxation techniques.

Psilocybin sessions. Drug sessions were conducted in an aesthetic living-room-like environment with two monitors present. Participants were instructed to consume a low-fat breakfast before coming to the research unit. A urine sample was taken to verify abstinence from common drugs of abuse (cocaine, benzodiazepines, and opioids including methadone). Participants who reported use of cannabis or dronabinol were instructed not

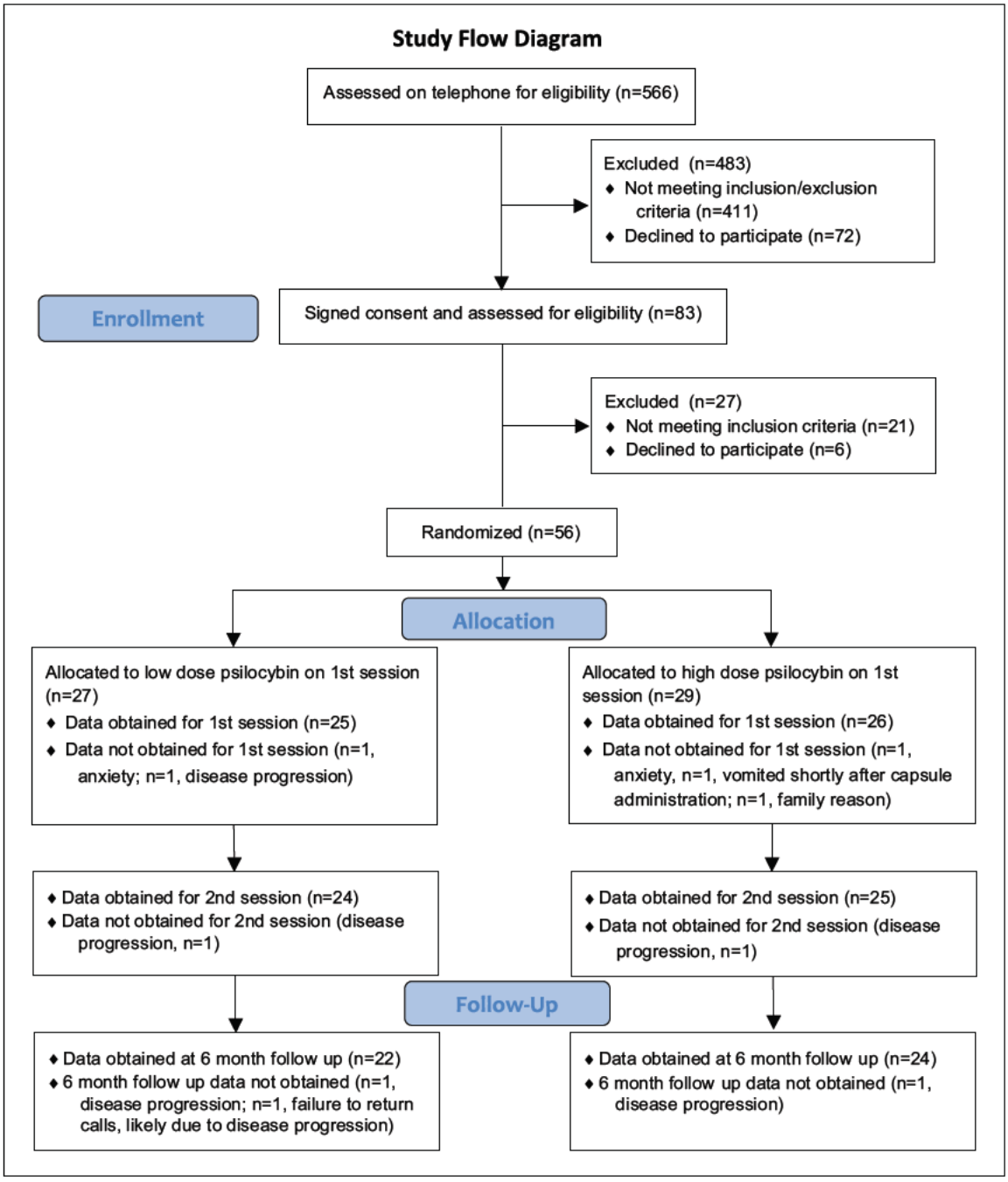

Figure 1. Flow diagram showing participation across the study.

to use for at least 24 h before sessions. Psilocybin doses were administered in identically appearing opaque, size 0 gelatin capsules, with lactose as the inactive capsule filler. For most of the time during the session, participants were encouraged to lie down on the couch, use an eye mask to block external visual distraction, and use headphones through which a music program was played. The same music program was played for all participants in both sessions. Participants were encouraged to focus their attention on their inner experiences throughout the session. Thus, there was no explicit instruction for participants to focus on their attitudes, ideas, or emotions related to their cancer. A more detailed description of the study room and procedures followed on session days is provided elsewhere (Griffiths et al., 2006; Johnson et al., 2008).

Instructions to participants and monitors to facilitate dose condition blinding and minimize expectancy effects. Expectancies, on part of both participants and monitors, are believed to play a large role in the qualitative effects of psilocybin-like drugs (Griffiths et al., 2006; Metzner et al., 1965). Although double-blind methods are usually used to protect against such effects, expectancy is likely to be significantly operative in a standard drug versus placebo design when the drug being evaluated produces highly discriminable effects and participants and staff

Table 1. Participant demographics for all participants and for both of the dose sequence groups separately+.

Measure	Low-Dose-1st (High-Dose-2nd) (*n*=25)	High-Dose-1st (Low-Dose-2nd) (*n*=26)	All Participants (*n*=51)
Gender (% female)	48%	50%	49%
Age in years (mean, SEM)	56.1 (2.3)	56.5 (1.8)	56.3 (1.4)
Race/Ethnicity			
White	92%	96%	94%
Black/African American	4%	4%	4%
Asian	4%	0%	2%
Education			
High school	4%	0%	2%
College	32%	58%	45%
Post-graduate	64%	42%	53%
Relationship status (married or living with partner)	72%	65%	69%
Lifetime use of hallucinogens			
Percent reporting any past use	56%	36%	45%
Years since last use (mean, SEM)	30.9 (3.2)	30.0 (4.5)	30.6 (2.6)
Recent use of cannabis or dronabiol			
Percent reporting recent use	52%	42%	47%
Users use per month (mean, SEM)	4.7 (1.6)	7.0 (2.1)	5.8 (1.3)
Cancer prognosis at time of enrollment			
Possibility of recurrence	32%	38%	35%
Recurrent/metastatic (>2yr anticipated survival)	32%	42%	37%
Recurrent/metastatic (<2yr anticipated survival)	36%	19%	27%
Psychiatric symptoms[a]			
Depressed mood	72%	65%	69%
Anxiety	68%	58%	63%
Prior use of medication for anxiety or depression[b]	52%	50%	51%

+There were no significant differences between the two dose sequence groups on any demographic variable (*t*-tests and chi-square tests with continuous and categorical variables, respectively).

[a]Psychiatric symptom classification was based on SCID (DSM-IV) diagnoses. All had a DSM-IV diagnosis: chronic adjustment disorder with anxiety (11 participants), chronic adjustment disorder with mixed anxiety and depressed mood (11), dysthymic disorder (5), generalized anxiety disorder (GAD) (5), major depressive disorder (MDD) (14), or a duel diagnosis of GAD and MDD (4), or GAD and dysthymic disorder (1). Depressed mood was defined as meeting criteria for MDD, dysthymic disorder, or adjustment disorder with anxiety and depressed mood, chronic. Anxiety was defined as meeting criteria for GAD, adjustment disorder with anxiety, chronic, or adjustment disorder with anxiety and depressed mood, chronic.

[b]Data in this row refer to percentage of participants who had received antidepressant or anxiolytic medication after the cancer diagnosis but had terminated the medication sometime before study enrollment because they had found it to be unsatisfactory.

know the specific drug conditions to be tested. For these reasons, in the present study a low dose of psilocybin was compared with a high dose of psilocybin, and participants and monitors were given instructions that obscured the actual dose conditions to be tested. Specifically, they were told that psilocybin would be administered in both sessions, the psilocybin doses administered in the two sessions might range anywhere from very low to high, the doses in the two sessions might or might not be the same, sensitivity to psilocybin dose varies widely across individuals, and that at least one dose would be moderate to high. Participants and monitors were further strongly encouraged to try to attain maximal therapeutic and personal benefit from each session.

Dose conditions. The study compared a high psilocybin dose (22 or 30 mg/70 kg) with a low dose (1 or 3 mg/70 kg) administered in identically appearing capsules. When this study was designed, we had little past experience with a range of psilocybin doses. We decreased the high dose from 30 to 22 mg/70 kg after two of the first three participants who received a high dose of 30 mg/70 kg were discontinued from the study (one from vomiting shortly after capsule administration and one for personal reasons). Related to this decision, preliminary data from a dose-effect study in healthy participants suggested that rates of psychologically challenging experiences were substantially greater at 30 than at 20 mg/70 kg (Griffiths et al., 2011). The low dose of psilocybin was decreased from 3 to 1 mg/70 kg after 12 participants because data from the same dose-effect study showed significant psilocybin effects at 5 mg/70 kg, which raised concern that 3 mg/70 kg might not serve as an inactive placebo.

Outcome measures

Cardiovascular measures and monitor ratings assessed throughout the session. Ten minutes before and 30, 60, 90, 120, 180, 240, 300, and 360 min after capsule administration, blood pressure, heart rate, and monitor ratings were obtained as described previously (Griffiths et al., 2006). The two session monitors completed the Monitor Rating Questionnaire, which involved rating or scoring several dimensions of the participant's behavior or mood. The dimensions, which are expressed as peak scores in Table 2, were rated on a 5-point scale from 0 to 4. Data were the mean of the two monitor ratings at each time-point.

Table 2. Peak effects on cardiovascular measures and session monitor ratings of participant behavior and mood assessed throughout the session[+].

Measure	Low dose	High dose
Cardiovascular measures (peak effects)		
Systolic blood pressure (mm Hg)	142.20 (2.45)	155.26 (2.87)***
Diastolic blood pressure (mm Hg)	82.90 (1.35)	89.68 (1.21)***
Heart rate (beats per minute)	78.86 (2.17)	84.06 (2.36)***
Session monitor ratings (peak effects)[a]		
Overall drug effect	1.37 (0.09)	2.90 (0.07)***
Unresponsive to questions	0.13 (0.07)	0.70 (0.12)***
Anxiety or fearfulness	0.50 (0.10)	0.93 (0.15)**
Distance from ordinary reality	0.94 (0.12)	2.68 (0.10)***
Ideas of reference/paranoid thinking	0.05 (0.03)	0.14 (0.05)***
Yawning	0.33 (0.11)	1.28 (0.26)***
Tearing/crying	0.66 (0.14)	2.01 (0.25)***
Nausea/vomiting	0.11 (0.04)	0.44 (0.10)**
Visual effects with eyes open	0.32 (0.09)	1.83 (0.17)***
Visual effects with eyes closed	0.93 (0.09)	1.75 (0.07)***
Spontaneous motor activity	1.12 (0.15)	1.86 (0.30)*
Restless/fidgety	0.83 (0.12)	1.28 (0.15)**
Joy/intense happiness	0.69 (0.12)	1.90 (0.14)***
Peace/harmony	1.08 (0.13)	2.01 (0.13)***
Psychological discomfort	0.34 (0.08)	0.91 (0.15)***
Physical discomfort	0.31 (0.08)	0.62 (0.11)**

[+]Data are means (SEM) for peak effects during sessions after low dose (n=50) or high dose (n=50) psilocybin collapsed across the two dose sequence groups. Asterisks indicate significant differences from the low dose (*p<0.05, **p<0.01, ***p<0.001).

[a]Maximum possible scores for all monitor ratings were 4 except for visual effects with eyes closed which was 2.

Subjective drug effect measures assessed 7 h after psilocybin administration. When psilocybin effects had subsided, participants completed four questionnaires: Hallucinogen Rating Scale (HRS) (Strassman et al., 1994); 5-Dimension Altered States of Consciousness (5D-ASC) (Dittrich, 1998); Mysticism Scale (Experience-specific 9-point scale) (Hood et al., 2001, 2009); and the States of Consciousness Questionnaire (SOCQ) (Griffiths et al., 2006). Thirty items on the SOCQ comprise the Mystical Experience Questionnaire (MEQ30), which was shown sensitive to mystical-type subjective effects of psilocybin in laboratory studies as well as survey studies of recreational use of psilocybin mushrooms (Barrett et al., 2015; MacLean et al., 2012). Four factor scores (Mystical, Positive mood, Transcendence of time and space, and Ineffability) and a mean total score (the mean of all 30 items) were assessed.

Therapeutically relevant measures assessed at Baseline, 5 weeks after each session, and 6-month follow-up. Seventeen measures focused on mood states, attitudes, disposition, and behaviors thought to be therapeutically relevant in psychologically distressed cancer patients were assessed at four time-points over the study: immediately after study enrollment (Baseline assessment), about 5 weeks (mean 37 days) after each session (Post-session 1 and 2 assessments), and about 6 months (mean 211 days) after session 2 (6-month follow-up).

The two primary therapeutic outcome measures were the widely used clinician-rated measures of depression, GRID-HAM-D-17 (ISCDD, 2003) and anxiety, HAM-A assessed with the SIGH-A (Shear et al., 2001). For these clinician-rated measures, a clinically significant response was defined as ⩾50% decrease in measure relative to Baseline; symptom remission was defined as ⩾50% decrease in measure relative to Baseline and a score of ⩽7 on the GRID-HAMD or HAM-A (Gao et al., 2014; Matza et al., 2010).

Fifteen secondary measures focused on psychiatric symptoms, moods, and attitudes: BDI, self-rated depression measure (Beck and Steer, 1987); HADS, self-rated separate measures of depression and anxiety, and a total score (Zigmond and Snaith, 1983); STAI, self-rated measure of state and trait anxiety separately (Spielberger, 1983); POMS, Total Mood Disturbance Subscale, self-rated dysphoric mood measure (McNair et al., 1992); BSI, self-rated psychiatric symptoms (Derogatis, 1992); MQOL, self-rated measure of overall quality of life (total score) and meaningful existence (existential subscale) during life-threatening illness (Cohen et al., 1995); LOT-R, self-rated optimism measure associated with illness (Scheier and Carver, 1985); LAP-R Death Acceptance, self-rated scale assessing absence of anxiety about death (Reker, 1992); Death Transcendence Scale, self-rated measure of positive attitudes about death (VandeCreek, 1999); Purpose in Life Test, self-rated measure of life meaningfulness (McIntosh, 1999); and LAP-R Coherence, self-rated scale assessing logically integrated understanding of self, others, and life in general (Reker, 1992).

Community observer-rated changes in participant behavior and attitudes assessed at Baseline, 5 weeks after Session 2, and 6-month follow-up. Structured telephone interviews with community observers (e.g. family members, friends, or work colleagues) provided ratings of participant attitudes and behavior reflecting healthy psychosocial functioning (Griffiths et al., 2011). The interviewer provided no information to the rater about the participant or the nature of the research study. The structured interview (Community Observer Questionnaire) consisted of asking the rater to rate the participant's behavior and attitudes using a 10-point scale (from 1 = not at all, to 10 = extremely) on 13 items reflecting healthy psychosocial functioning: inner peace; patience; good-natured humor/playfulness; mental flexibility; optimism; anxiety (scored negatively); interpersonal perceptiveness and caring; negative expression of anger (scored negatively); compassion/social concern; expression of positive emotions (e.g. joy, love, appreciation); self-confidence; forgiveness of others; and forgiveness of self. On the first rating occasion, which occurred soon after acceptance into the study, raters were instructed to base their ratings on observations of and conversations with the participant over the past 3 months. On two subsequent assessments, raters were told their previous ratings and were instructed to rate the participant based on interactions over the last month (post-session 2 assessment) or since beginning in the study (6-month follow-up). Data from each interview with each rater were calculated as a total score. Changes in each participant's behavior and attitudes after drug sessions were expressed as a mean change score (i.e. difference score) from the baseline rating across the raters. Of 438 scheduled ratings by community observers, 25 (<6%) were missed due to failure to return calls or to the rater not having contact with the participant over the rating period.

Spirituality measures assessed at Baseline, 5 weeks after Session 2, and 6-month follow-up. Three measures of spirituality were assessed at three time-points: Baseline, 5 weeks after session 2, and at the 6-month follow-up: FACIT-Sp, a self-rated measure of the spiritual dimension of quality of life in chronic illness (Peterman et al., 2002) assessed on how the participant felt "on average"; Spiritual-Religious Outcome Scale, a three-item measure used to assess spiritual and religious changes during illness (Pargament et al., 2004); and Faith Maturity Scale, a 12-item scale assessing the degree to which a person's priorities and perspectives align with "mainline" Protestant traditions (Benson et al., 1993).

Persisting effects of the psilocybin session assessed 5 weeks after each session and 6-month follow-up. The Persisting Effects Questionnaire assessed self-rated positive and negative changes in attitudes, moods, behavior, and spiritual experience attributed to the most recent psilocybin session (Griffiths et al., 2006, 2011). At the 6-month follow-up, the questionnaire was completed on the basis of the high-dose session, which was identified as the session in which the participant experienced the most pronounced changes in their ordinary mental processes. Twelve subscales (described in Table 8) were scored.

The questionnaire included three final questions (see Griffiths et al. 2006 for more specific wording): (1) How personally meaningful was the experience? (rated from 1 to 8, with 1 = no more than routine, everyday experiences; 7 = among the five most meaningful experiences of my life; and 8 = the single most meaningful experience of my life). (2) Indicate the degree to which the experience was spiritually significant to you? (rated from 1 to 6, with 1 = not at all; 5 = among the five most spiritually significant experiences of my life; 6 = the single most spiritually significant experience of my life). (3) Do you believe that the experience and your contemplation of that experience have led to change in your current sense of personal well-being or life satisfaction? (rated from +3 = increased very much; +2 = increased moderately; 0 = no change; –3 = decreased very much).

Statistical analysis

Differences in demographic data between the two dose sequence groups were examined with *t*-tests and chi-square tests with continuous and categorical variables, respectively.

Data analyses were conducted to demonstrate the appropriateness of combining data for the 1 and 3 mg/70 kg doses in the low-dose condition and for including data for the one participant who received 30 mg/70 kg. To determine if the two different psilocybin doses differed in the low-dose condition, *t*-tests were used to compare participants who received 3 mg/70 kg ($n = 12$) with those who received 1 mg/70 kg ($n = 38$) on participant ratings of peak intensity of effect (HRS intensity item completed 7 h after administration) and peak monitor ratings of overall drug effect across the session. Because neither of these were significantly different, data from the 1 and 3 mg/70 kg doses were combined in the low-dose condition for all analyses.

Of the 50 participants who completed the high-dose condition, one received 30 mg/70 kg and 49 received 22 mg/70 kg. To determine if inclusion of the data from the one participant who received 30 mg/70 kg affected conclusions about the most therapeutically relevant outcome measures, the analyses for the 17 measures shown in Tables 4 and 5 were conducted with and without that participant. Because there were few differences in significance (72 of 75 tests remained the same), that participant's data were included in all the analyses.

To examine acute drug effects from sessions, the drug dose conditions were collapsed across the two dose sequence groups. The appropriateness of this approach was supported by an absence of any significant group effects and any group-by-dose interactions on the cardiovascular measures (peak systolic and diastolic pressures and heart rate) and on several key monitor- and participant-rated measures: peak monitor ratings of drug strength and joy/intense happiness, and end-of-session participant ratings on the Mysticism Scale.

Six participants reported initiating medication treatment with an anxiolytic (2 participants), antidepressant (3), or both (1) between the Post-session 2 and the 6-month follow-up assessments. To determine if inclusion of these participants affected statistical outcomes in the analyses of the 6-month assessment, the analyses summarized in Tables 4, 5, 6, 7 and 8 were conducted with and without these six participants. All statistical outcomes remained identical. Thus, data from these six participants were retained in the data analyses.

For cardiovascular measures and monitor ratings assessed repeatedly during sessions, repeated measures regressions were conducted in SAS PROC MIXED using an AR(1) covariance structure and fixed effects of dose and time. Planned comparison *t*-tests were used to assess differences between the high- and low-dose condition at each time-point.

Peak scores for cardiovascular measures and monitor ratings during sessions were defined as the maximum value from pre-capsule to 6 h post-capsule. These peak scores and the end-of-session ratings (Tables 2 and 3) were analyzed using repeated measures regressions in SAS PROC MIXED with a CS covariance structure and fixed effects of group and dose.

For the analyses of continuous measures described below, repeated measures regressions were conducted in SAS PROC MIXED using an AR(1) covariance structure and fixed effects of group and time. Planned comparison *t*-tests (specified below) from these analyses are reported. For dichotomous measures, Friedman's Test was conducted in SPSS for both the overall analysis and planned comparisons as specified below. All results are expressed as unadjusted scores.

For the measures that were assessed in the two dose sequence groups at Baseline, Post-session 1, Post-session 2, and 6 months (Tables 4 and 5), the following planned comparisons most relevant to examining the effects of psilocybin dose were conducted: Between-group comparisons at Baseline, Post 1, and Post 2; and within-group comparisons of Baseline versus Post 1 in both dose sequence groups, and Post 1 versus Post 2 in the Low-Dose-1st (High-Dose-2nd) Group. A planned comparison between Baseline and 6 months collapsed across groups was also conducted. Effects sizes were calculated using Cohen's *d*.

For measures assessed only at Baseline, Post 2, and 6 months (Table 7), between-group planned comparisons were conducted at Baseline, Post 2, and 6 months. Because measures assessed only at these time-points cannot provide information about the psilocybin dose, data were collapsed across the two dose sequence groups and planned comparisons were conducted comparing Baseline with Post 2 and Baseline with 6 months.

Table 3. Participant ratings on questionnaires completed 7 hours after psilocybin administration+.

Questionnaire and subscale description	Low dose (post-session)	High dose (post-session)
Hallucinogen Rating Scale (HRS)		
Intensity	36.47 (2.78)	63.76 (2.34)***
Somesthesia	15.38 (1.55)	35.62 (2.75)***
Affect	23.79 (2.13)	44.60 (2.54)***
Perception	12.92 (1.76)	41.18 (2.78)***
Cognition	18.88 (2.09)	43.08 (2.54)***
Volition	30.81 (2.02)	37.06 (1.88)*
5 Dimension Altered States of Consciousness (5D-ASC)		
Oceanic boundlessness (OBN)	26.86 (3.73)	63.99 (3.78)***
Dread of ego dissolution (DED)	6.89 (1.50)	19.21 (2.38)***
Visionary restructuralization (VRS)	22.41 (2.99)	61.16 (3.48)***
Auditory alterations (AUA)	6.72 (1.87)	14.88 (2.18)***
Vigilance reduction (VIR)	22.74 (2.70)	30.85 (2.24)**
Mystical Experience Questionnaire (MEQ30)		
Mystical	24.34 (3.83)	59.58 (4.22)***
Transcendence of time and space	22.38 (2.90)	62.08 (3.38)***
Positive mood	35.84 (4.00)	69.82 (3.82)***
Ineffability	30.80 (4.49)	74.46 (3.67)***
Total	26.90 (3.44)	63.64 (3.56)***
Mysticism Scale (M scale)		
Interpretation	48.95 (3.54)	71.45 (2.24)***
Introvertive	44.53 (3.21)	71.20 (2.14)***
Extrovertive	37.48 (3.19)	64.58 (2.81)***
Total	49.36 (3.51)	77.38 (2.40)***

+All data are expressed as a percentage of maximum possible score. Data are means (1 SEM) for questionnaires completed 7 h after the low-dose (n = 50) and high-dose (n = 50) sessions collapsed across the two dose sequence groups. Asterisks indicate significant differences from the low dose (*p<0.05, **p<0.01, ***p<0.001).

For participant ratings of persisting effects attributed to the session (e.g. Table 8), planned comparisons for continuous and dichotomous measures were conducted between: (1) ratings at 5 weeks after the low versus high-dose sessions; (2) ratings of low dose at 5 weeks versus ratings of high dose at the 6-month follow-up; (3) ratings of high dose at 5 weeks versus ratings of high dose at the 6-month follow-up.

As described above, clinician-rated measures of depression (GRID-HAMD) and anxiety (HAM-A) were analyzed as continuous measures. In addition for both measures, a clinically significant response was defined as ⩾50% decrease in measure relative to Baseline; symptom remission was defined as ⩾50% decrease in measure relative to Baseline and a score of ⩽7. Planned comparisons were conducted via independent z-tests of proportions between the two dose sequence groups at Post-session 1, Post-session 2, and 6 months. To determine if effects were sustained at 6 months, planned comparisons were also conducted via dependent z-tests of proportions between Post-session 2 versus 6 months in the Low-Dose-1st (High-Dose-2nd) Group, and between Post-session 1 versus 6 months in the High-Dose-1st (Low-Dose-2nd) Group.

Exploratory analyses used Pearson's correlations to examine the relationship between total scores on the Mystical Experience Questionnaire (MEQ30) assessed at the end of session 1 and enduring effects assessed 5 weeks after session 1. The Post-session 1 measures were ratings on three items from the Persisting Effects Questionnaire (meaningfulness, spiritual significance, and life satisfaction) and 17 therapeutically relevant measures assessed at Baseline and Post 1 (Tables 4 and 5) expressed as difference from baseline scores. Significant relationships were further examined using partial correlations to control for end-of-session participant-rated "Intensity" (item 98 from the HRS). To examine MEQ30 scores as a mediator of the effect of psilocybin dose on therapeutic effects, a bootstrap analysis was done using the PROCESS macro (Hayes, 2013) in SPSS. Bootstrapping is a non-parametric method appropriate for small samples, which was used to estimate 95% confidence intervals for the mediation effect. The PROCESS macro also calculated direct effects on outcome for both group effects and MEQ30.

Results

Adverse effects

No serious adverse events attributed to psilocybin administration occurred. A number of adverse events occurred during psilocybin sessions, none of which were deemed to be serious. Except as noted below, all of these adverse events had resolved fully by the end of the sessions. Consistent with previous research (Griffiths et al., 2006, 2011), there were transient moderate increases in systolic and/or diastolic blood pressure after psilocybin. In this study, an episode of elevated systolic blood pressure (>160 mm Hg at one or more time-point) occurred in 34% of participants in the high-dose session and 17% of participants in the low-dose session. An episode of elevated diastolic blood pressure (>100 mm Hg at one or more time-point) occurred in 13% of participants in the high-dose session and 2% of participants in the low-dose session. None of these episodes met criteria for medical intervention. Nausea or vomiting occurred in 15% of participants in the high-dose session and none in the low-dose session. An episode of physical discomfort (any type) occurred in 21% of participants in the high-dose session and 8% in the low-dose session. Also consistent with previous research (Griffiths et al., 2006, 2011), transient episodes of psychological distress during psilocybin sessions (as rated by session monitors) were more common after the high dose than the low dose. Psychological discomfort (any type) occurred in 32% of participants in the high-dose session and 12% in the low-dose session. An episode of anxiety occurred in 26% of participants in the high-dose session and 15% in the low-dose session. One participant had a transient episode of paranoid ideation (2% of high-dose sessions). There were no cases of hallucinogen persisting perception disorder or prolonged psychosis. One participant reported mild headache starting toward the end of the high-dose session and lasting until 9 p.m. that evening. Of the 11 participants for whom headache was assessed on the day after sessions, two reported a delayed moderate headache after the high-dose session.

Integrity of blinding procedures

After all psilocybin sessions had been completed, the eight study staff members who had served as primary monitors or as assistant monitors for four or more participants completed a questionnaire

Table 4. Effects of psilocybin on the 11 therapeutically relevant outcome measures assessed at Baseline, Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6 months follow-up that fulfilled conservative criteria for demonstrating an effect of psilocybin+.

Measure	Group	Assessment time-point			
		Baseline[a]	Post-session 1[b]	Post-session 2[c]	6 months[d]
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	22.32 (0.88)	*14.80 (1.45)*	6.50 (0.86)***	6.95 (1.24)
	High-Dose-1st (Low-Dose-2nd)	22.84 (0.97)	*6.64 (1.04)***	6.52 (1.44)	6.23 (1.30)
Beck Depression Inventory (BDI)	Low-Dose-1st (High-Dose-2nd)	18.40 (1.09)	*12.92 (1.58)*	8.17 (1.24)***	8.00 (1.50)
	High-Dose-1st (Low-Dose-2nd)	17.77 (1.61)	*7.00 (1.39)***	5.80 (1.41)	6.17 (1.26)
HADS Depression	Low-Dose-1st (High-Dose-2nd)	9.48 (0.71)	*6.04 (0.79)*	4.57 (0.73)*	4.64 (0.72)
	High-Dose-1st (Low-Dose-2nd)	9.81 (0.69)	*3.92 (0.74)**	4.28 (0.89)	3.46 (0.66)
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	25.68 (0.89)	*16.64 (1.53)*	8.92 (1.14)***	7.95 (1.19)
	High-Dose-1st (Low-Dose-2nd)	25.73 (1.11)	*8.48 (1.16)****	7.52 (1.27)	7.04 (1.17)
STAI-Trait Anxiety	Low-Dose-1st (High-Dose-2nd)	47.46 (1.62)	*40.48 (2.11)*	35.48 (2.05)**	36.83 (2.08)
	High-Dose-1st (Low-Dose-2nd)	47.73 (1.91)	*34.64 (1.84)**	34.28 (2.25)	35.32 (2.18)
POMS Total Mood Disturbance	Low-Dose-1st (High-Dose-2nd)	51.72 (6.35)	42.48 (7.72)	21.09 (5.81)***	23.50 (6.57)
	High-Dose-1st (Low-Dose-2nd)	56.93 (5.33)	*18.96 (5.78)***	17.14 (6.35)	12.52 (5.36)
Brief Symptom Inventory (BSI)	Low-Dose-1st (High-Dose-2nd)	41.76 (4.40)	*33.74 (4.47)*	26.08 (4.53)*	23.50 (3.85)
	High-Dose-1st (Low-Dose-2nd)	40.19 (3.71)	*18.08 (3.62)***	16.48 (3.77)	14.35 (3.35)
MQOL (Overall Quality of Life)	Low-Dose-1st (High-Dose-2nd)	5.69 (0.24)	6.17 (0.32)	6.90 (0.34)**	6.88 (0.37)
	High-Dose-1st (Low-Dose-2nd)	5.32 (0.29)	*7.14 (0.29)**	7.46 (0.34)	7.65 (0.36)
MQOL (Meaningful Existence)	Low-Dose-1st (High-Dose-2nd)	6.03 (0.30)	6.10 (0.39)	7.30 (0.35)***	7.29 (0.31)
	High-Dose-1st (Low-Dose-2nd)	5.43 (0.29)	*7.23 (0.33)**	7.30 (0.38)	7.62 (0.35)
LAP-R Death Acceptance	Low-Dose-1st (High-Dose-2nd)	28.05 (2.04)	29.14 (2.25)	34.95 (1.92)***	34.95 (1.52)
	High-Dose-1st (Low-Dose-2nd)	29.09 (2.07)	*36.17 (1.59)**	35.13 (1.90)	36.25 (1.59)
LOT-R (Optimism)	Low-Dose-1st (High-Dose-2nd)	13.56 (0.97)	13.60 (1.23)	15.96 (1.12)**	16.68 (1.14)
	High-Dose-1st (Low-Dose-2nd)	14.15 (0.97)	*17.23 (0.67)**	17.16 (0.99)	17.43 (0.92)

+Numerical data show means (SEM) for outcome measures in the two dose sequence groups: (1) those that received a low dose on the 1st session and a high dose on the 2nd (n = 25, 25, 24, and 22 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively), and (2) those that received a high dose on 1st session and a low dose on the 2nd (n = 26, 25 or 26, 25, and 24 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively). Data are shown for the 11 measures that fulfilled the most conservative criteria for demonstrating psilocybin effects (i.e. showing a significant between-group difference at the Post-session 1 assessment as well as a difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group). Results for the measures not fulfilling these criteria are shown in Table 5.

[a]In this column (Baseline), there were no significant differences between groups.

[b]In this column, italic font indicates a within-group significant difference from Baseline (p<.05, planned comparison); asterisks indicate significant differences between groups (*p<0.05, **p<0.01, ***p<0.001, planned comparisons); between groups effect size (Cohen's d as absolute values) for the 11 measures from top to bottom were: 1.30, 0.81, 0.56, 1.23, 0.60, 0.70, 0.78, 0.65, 0.65, 0.97, and 0.75.

[c]In this column, there were no significant differences between groups; asterisks indicate significant differences between the Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group (*p<0.05, **p<0.01, ***p<0.001, planned comparisons); effect size (Cohen's d as absolute values) for the 11 measures from top to bottom were: 1.33, 0.69, 0.40, 1.10, 0.50, 0.64, 0.35, 0.46, 0.66, 0.68, and 0.41.

[d]The difference between Baseline and 6 months, collapsed across groups, was significant for all 11 measures (p<0.001, planned comparison); effect size (Cohen's d as absolute values) for the 11 measures from top to bottom were: 2.98,1.63, 1.65, 3.40, 1.20, 1.26, 1.17, 1.14, 1.12, 0.84, and 0.66.

that asked about their understanding of the experimental design. Although all correctly believed that psilocybin had been administered, five of eight made incorrect inferences about the study design or procedures, including possible administration of three or more dose levels of psilocybin across different participants (four monitors), an inactive placebo (one monitor), other psychoactive compounds such as dextromethorphan (one monitor), or only low psilocybin doses (one monitor).

At the end of each session day, monitors rated their guess of the magnitude of drug dose administered in the capsule that day on a 10 cm line. Although, as expected, the mean (±SE) monitor rating of the dose magnitude of the high psilocybin dose was significantly larger than the low dose (7.0±0.29 vs. 1.7±0.21, p<0.001, planned comparison), the distributions of ratings overlapped, with more than 13% of the high-dose sessions being rated as 4 or less and more than 12% of the low-dose sessions being rated as 4 or more. Overall, we conclude that the blinding procedures provided some protection against a priori monitor expectancy strongly determining outcomes of the psilocybin dose manipulation.

Outcome measures

Psilocybin produced orderly dose- and time-related increases on blood pressure, heart rate, and all 16 monitor-rated dimensions of the participant's behavior or mood assessed throughout sessions, with a generally similar time-course in both dose conditions (see Figure 2 for illustrative time-course measures). Significant differences between the dose conditions generally first occurred at 30- or 60-min, with the high dose usually showing peak effects from 90–180 min and decreasing toward pre-drug levels over the remainder of the session. Table 2 shows mean peak effects for these measures.

End-of-session measures that assessed subjective experiences during the session were significantly greater after the high than the low dose (Table 3).

Table 5. Effects of psilocybin on six therapeutically relevant outcome measures assessed at Baseline, Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6 months that did not fulfill conservative criteria for demonstrating an effect of psilocybin+.

Measure	Group	Assessment time-point			
		Baseline[a]	Post-session 1[b]	Post-session 2[c]	6 months[d]
HADS Total	Low-Dose-1st (High-Dose-2nd)	20.52 (0.92)	*12.04 (1.18)*	9.17 (1.15)*	9.32 (1.22)
	High-Dose-1st (Low-Dose-2nd)	20.88 (0.89)	*9.31 (1.29)*	8.96 (1.53)	8.17 (1.16)
HADS Anxiety	Low-Dose-1st (High-Dose-2nd)	11.04 (0.60)	*6.00 (0.59)*	4.91 (0.60)	4.68 (0.67)
	High-Dose-1st (Low-Dose-2nd)	11.08 (0.53)	*5.38 (0.78)*	4.68 (0.75)	4.71 (0.65)
STAI State Anxiety	Low-Dose-1st (High-Dose-2nd)	42.00 (1.76)	*37.48 (2.49)*	32.83 (2.21)*	32.73 (2.38)
	High-Dose-1st (Low-Dose-2nd)	45.77 (1.98)	*34.36 (2.17)*	31.56 (2.02)	30.25 (1.98)
Death Transcendence Scale	Low-Dose-1st (High-Dose-2nd)	122.12 (4.39)	*127.66 (3.92)*	136.00 (3.62)**	133.36 (3.91)
	High-Dose-1st (Low-Dose-2nd)	117.85 (3.34)	*128.46 (3.99)*	127.25 (4.09)	128.96 (4.07)
Purpose in Life	Low-Dose-1st (High-Dose-2nd)	96.16 (3.32)	*101.80 (3.78)*	106.92 (3.63)*	108.00 (3.36)
	High-Dose-1st (Low-Dose-2nd)	91.04 (3.43)	*106.19 (3.04)*	107.00 (3.73)	108.08 (3.71)
LAP-R Coherence	Low-Dose-1st (High-Dose-2nd)	35.25 (2.36)	*38.14 (2.52)*	43.00 (2.31)*	43.25 (2.09)
	High-Dose-1st (Low-Dose-2nd)	30.86 (1.91)	*36.83 (2.01)*	39.30 (2.05)	40.25 (1.93)

+Numerical data show means (1 SEM) for primary outcome measures in the two dose sequence groups: (1) those that received a low dose on the 1st session and a high dose on the 2nd (n = 25, 25, 24, and 22 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively), and (2) those that received a high dose on 1st session and a low dose on the 2nd (n = 26, 26, 25, and 24 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively). Data are shown for the six measures that did not fulfill the most conservative criteria for demonstrating psilocybin effects (i.e. did not show a significant between-group difference at the Post-session 1 assessment as well as a significant difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group).

[a]In this column, there were no significant differences between groups.

[b]In this column, italic font indicates a within-group significant difference from Baseline (p<0.05, planned comparison); there were no significant between-group differences.

[c]In this column, there were no significant differences between groups; asterisks indicate significant differences between the Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group (*p<0.05, **p<0.01, planned comparisons); effect size (Cohen's d as absolute values) for the five significant measures (HADS total, STAI State Anxiety, Death Transcendence Scale, Purpose in Life, and LAP-R Coherence, respectively were: 0.51, 0.41, 0.46, 0.28, and 0.49.

[d]The difference between Baseline and 6 months, collapsed across groups, was significant for all six measures (p<0.001, planned comparison); effect size (Cohen's d as absolute values) for the six measures from top to bottom were: 2.34, 2.15, 1.25, 0.58, 0.85, and 0.90.

Table 6. Percentage of participants with clinically significant response rate and symptom remission rate as assessed with the clinician-rated measures of depression and anxiety+[a].

Measure	Group	Assessment time-point					
		Post-session 1		Post-session 2		6 months[b]	
		Clinical response	Symptom remission	Clinical response	Symptom remission	Clinical response	Symptom remission
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	32%	16%	75%	58%	77%	59%
	High-Dose-1st (Low-Dose-2nd)	92%***	60%**	84%	68%	79%	71%
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	24%	12%	83%	42%	82%	50%
	High-Dose-1st (Low-Dose-2nd)	76%***	52%**	80%	60%	83%	63%

+ Data are percentage of participants fulfilling criteria at Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6 months. Clinical response was defined as ⩾50% decrease in measure relative to Baseline; Symptom remission was defined as ⩾50% decrease in measure relative to Baseline and a score of ⩽7 on GRID-HAMD-17 or HAM-A. For the Post-session 1, Post-session 2, and 6-month time-points, respectively, the number of participants was 25, 24, and 22 in the Low-Dose-1st (High-Dose-2nd) Group, and 25, 25, and 24 in the High-Dose-1st (Low-Dose-2nd) Group.

[a]Within each data column, asterisks indicate significant differences between groups (*p<0.05, **p<0.01, ***p<0.001, planned comparisons, z-tests).

[b]Effects of psilocybin on response and remission were sustained at 6 months as indicated by an absence of significant difference (p>0.05, planned comparisons, z-tests) between (1) Post-session 2 vs. 6 months in the Low-Dose-1st (High-Dose-2nd) Group and (2) Post-session 1 vs. 6 months in the High-Dose-1st (Low-Dose-2nd) Group. Overall response and remission rates were somewhat higher at 6 months when data were excluded for the six participants who initiated treatment with an antidepressant or anxiolytic between Post-session 2 and 6 months: on the GRID-HAMD-17 mean response and remission rate across the two dose sequence groups at 6 months increased from 78% to 83% and from 65% to 68%, respectively. On the HAM-A these rates increased from 83% to 85% and from 57% to 60%, respectively.

Psilocybin produced large and sustained effects on the two primary clinician-rated therapeutically relevant outcome measures as well as most of the secondary measures assessed at Baseline, 5 weeks after each session, and at 6-month follow-up. Of the 17 measures assessed, 16 showed significant effects (i.e. a between-group difference at the Post-session 1 assessment and/or

Table 7. Community observer ratings of participant attitudes and behavior, and three measures of spirituality assessed at Baseline, Post-session 2 (5 weeks after Session 2), and 6 months, collapsed across the two drug sequence groups*.

Measure	Assessment time-point		
	Baseline	Post-session 2[a]	6 months[b]
Community observer ratings of positive changes in attitudes & behavior			
Total score	81.62 (1.61)	93.79 (1.70)***	94.41 (1.66)***
FACIT-Sp – Spiritual well-being in chronic illness			
Total score (% of maximum score)	44.92 (2.71)	68.13 (3.62)***	70.79 (3.17)***
Faith Maturity Scale			
Total score (% of maximum score)	49.73 (2.71)	53.94 (3.39)*	55.56 (3.29)*
Spiritual/Religious Outcome Scale			
Total score (% maximum score)	48.53 (3.97)	64.67 (3.54)***	63.41 (3.80)***

Numerical data show means (1 SEM) for outcome measures collapsed across the two dose sequence groups (n = 51, 50, and 46 at Baseline, Post-session 2, and 6 months, respectively). The two dose sequence groups were not significantly different from each other at Baseline, Post-session 2, and 6-month assessments (planned comparisons). Asterisks indicate significant differences from Baseline (p<0.05, **p<0.01, ***p<0.001, planned comparisons).
[a]In this column, effect size (Cohen's d as absolute values) for the four measures from top to bottom were: 1.06, 1.03, 0.20, 0.61.
[b]In this column, effect size (Cohen's d as absolute values) for the four measures from top to bottom were: 1.14, 1.28, 0.28, and 0.55.

Table 8. Participant ratings of persisting effects attributed to the session on ratings completed 5 weeks after the low-dose and high-dose psilocybin sessions, and, again, retrospectively for the high-dose session 6 months after the second session+.

Questionnaire and subscale description	Assessment time-point		
	Low dose (5 weeks)	High dose (5 weeks)	High dose 6-month follow-up
Persisting Effects Questionnaire (% of maximum score)			
Positive attitudes about life	39.57 (3.91)	57.78 (3.10)***	61.17 (3.51)***
Negative attitudes about life	3.82 (0.99)	5.08 (1.54)	3.18 (0.96)
Positive attitudes about self	35.16 (3.80)	50.70 (3.46)***	54.78 (3.37)***
Negative attitudes about self	3.89 (0.86)	4.80 (1.43)	3.52 (1.16)
Positive mood changes	36.85 (3.99)	49.06 (3.45)***	55.32 (3.58)***
Negative mood changes	3.42 (1.18)	5.42 (1.57)	3.00 (1.18)
Altruistic/positive social effects	35.60 (3.79)	47.42 (3.49)***	51.11 (3.69)***
Antisocial/negative social effects	3.55 (1.11)	3.73 (1.06)	2.51 (0.90)
Positive behavior changes	48.40 (4.66)	59.60 (4.02)***	64.78 (4.03)***
Negative behavior changes	1.60 (1.27)	3.60 (1.97)	0.87 (0.61)
Increased spirituality	37.07 (4.31)	52.48 (3.88)***	57.43 (4.17)***
Decreased spirituality	1.68 (0.63)	1.88 (0.68)	1.27 (0.39)
How personally meaningful was the experience? (maximum score=8)	4.62 (0.31)	6.38 (0.20)***	6.65 (0.18)***
Top 5 most meaningful of life, including single most (% of participants)	24%	62%***	67.4%***
How spiritually significant was the experience? (maximum score=6)	3.16 (0.24)	4.46 (0.19)***	4.78 (0.17)***
Top 5 most spiritually significant of life, including single most (% of participants)	24%	66%***	69.6%***
Did the experience change your sense of well-being or life satisfaction? (maximum score=3)	1.50 (0.19)	2.20 (0.16)***	2.33 (0.14)***
Increased well-being or life satisfaction moderately or very much (% of participants)	52%	86%***	82.6%***

+Except where noted, numerical data show means (1 SEM) for persisting effects ratings 5 weeks after the low-dose session (n = 50), 5 weeks after the high-dose session (n = 50), and, again, retrospectively for the high-dose session 6 months after the second session (n = 46). There were no significant differences between ratings of the high dose at 5 weeks after the session vs. the 6-month follow-up. Asterisks indicate significant differences from ratings obtained 5 weeks after the low dose session (*p<0.05, **p<0.01, ***p<0.001, planned comparisons).

a difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st Group). Conservative criteria for concluding that psilocybin dose affected these outcomes is to consider only those measures that showed both a between-group difference at Post-session 1 and a difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st

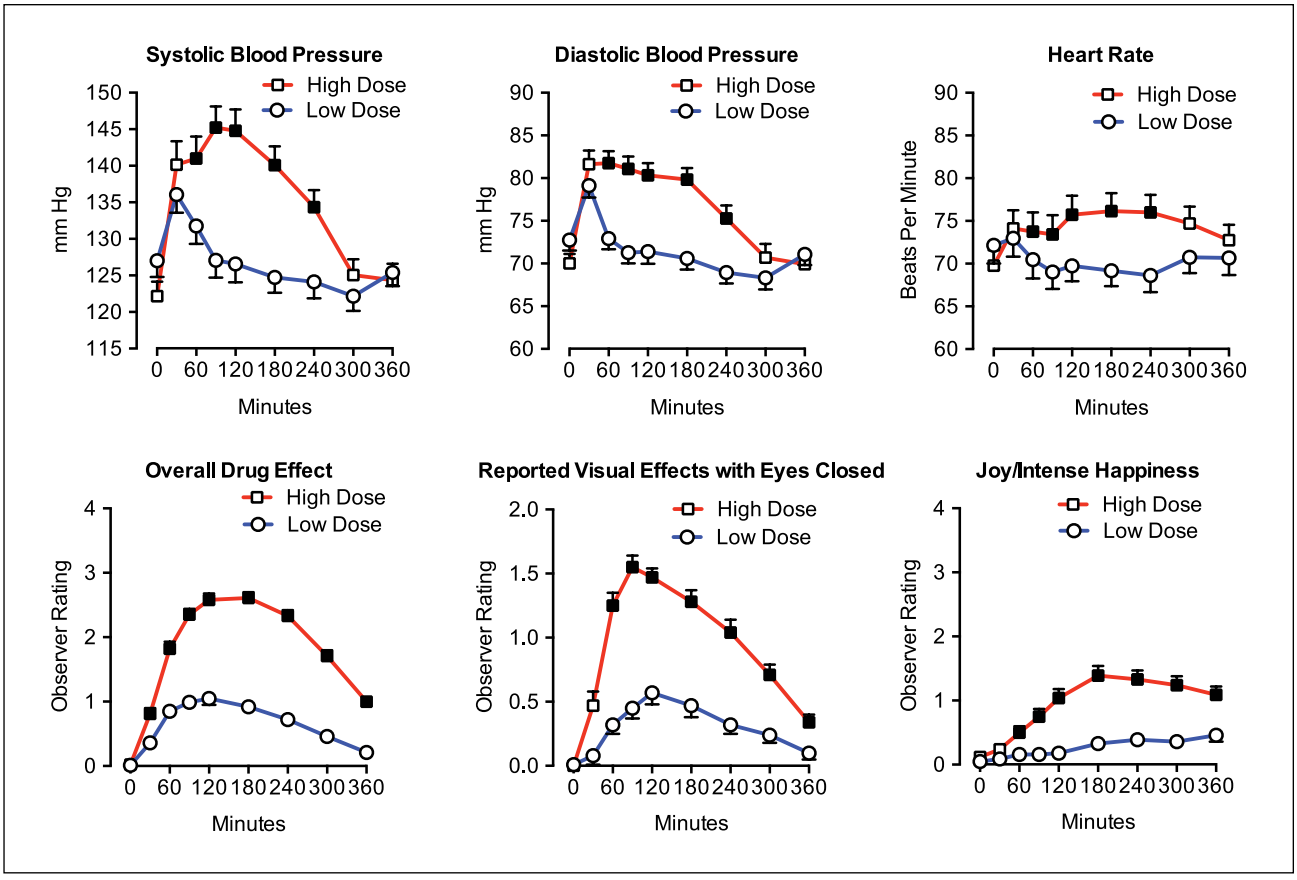

Figure 2. Within-session time-course of psilocybin effects on cardiovascular and observer-rated measures.
Cardiovascular (systolic and diastolic blood pressure, and heart rate) and observer (i.e. monitor)-rated overall drug effect, visual effects with eyes closed (as described by the participant), and joy/intense happiness. Data points show means; brackets indicate 1 SEM; circles show data after the low dose (n = 50); squares show data after the high dose (n = 50). Filled squares indicate the dose conditions were significantly different at the indicated time-point (p<0.05, planned comparisons). Y-axes for observer ratings show maximum possible scores.

Group. Table 4 shows data for the 11 measures that fulfilled these criteria and Figure 3 shows results graphically for nine of these measures. For the 11 measures, the mean effect size (Cohen's d) for the between-group difference at the Post-session 1 assessment was 0.82, for the within-group difference between Post-session 1 and Post-session 2 in the Low-Dose-1st Group was 0.66, and, for both groups combined, the difference between Baseline and 6 months was 1.55 (see Table 4 footnotes).

Table 5 presents results from six therapeutically relevant outcome measures that did not fulfill conservative criteria for demonstrating an effect of psilocybin. Although none of the measures showed a significant difference between groups at Post-session 1, five of the six showed a significant difference between Post-session 1 and Post-session 2 in the Low-Dose-1st (High-Dose-2nd) Group, and all six measures showed large significant changes in a therapeutically relevant direction (decreases in negative affect and increases in positive attitudes about death and life meaning and coherence) from Baseline to 6-Month Follow-up (mean effect size 1.35).

Rates of clinically significant response and symptom remission for the two primary outcome measures of clinician-rated symptoms of depression (GRID-HAMD-17) and anxiety (HAM-A) showed large effects of psilocybin that were sustained at 6 months (Table 6, Figure 4). For instance, 5 weeks after Session 1, 92% of participants in the High-Dose-1st Group showed a clinically significant response (i.e. ⩾50% decrease relative to Baseline) on the GRID-HAMD-17 compared with a 32% response rate in the Low-Dose-1st Group. At 6 months 79% of those in the High-Dose-1st Group continued to show a clinically significant response. Likewise, these percentages for the HAM-A were 76% and 24%, respectively, for the High-Dose 1st Group and Low-Dose-1st Group 5 weeks after Session 1, and 83% for the High-Dose-1st at 6 months. An analogous pattern of results was shown for symptom remission to normal range (i.e. ⩾50% decrease relative to Baseline and a score of ⩽7 on GRID-HAMD-17 or HAM-A), with rates of symptom remission of 60% and 52% for depression and anxiety, respectively, 5 weeks after the high psilocybin dose in Session 1, and with rates of 71% and 63%, respectively, sustained at 6 months. Collapsing across the two dose sequence groups, the overall rate of clinical response at 6 months was 78% and 83% for depression and anxiety, respectively, and the overall rate of symptom remission at 6 months for all participants was 65% and 57%, respectively.

Community observer ratings showed significant positive changes in participants' attitudes and behavior at the two post-psilocybin assessment time-points (Table 7). All three measures of spirituality showed similar increases (Table 7). As with the measures shown in Table 4, these measures show significant

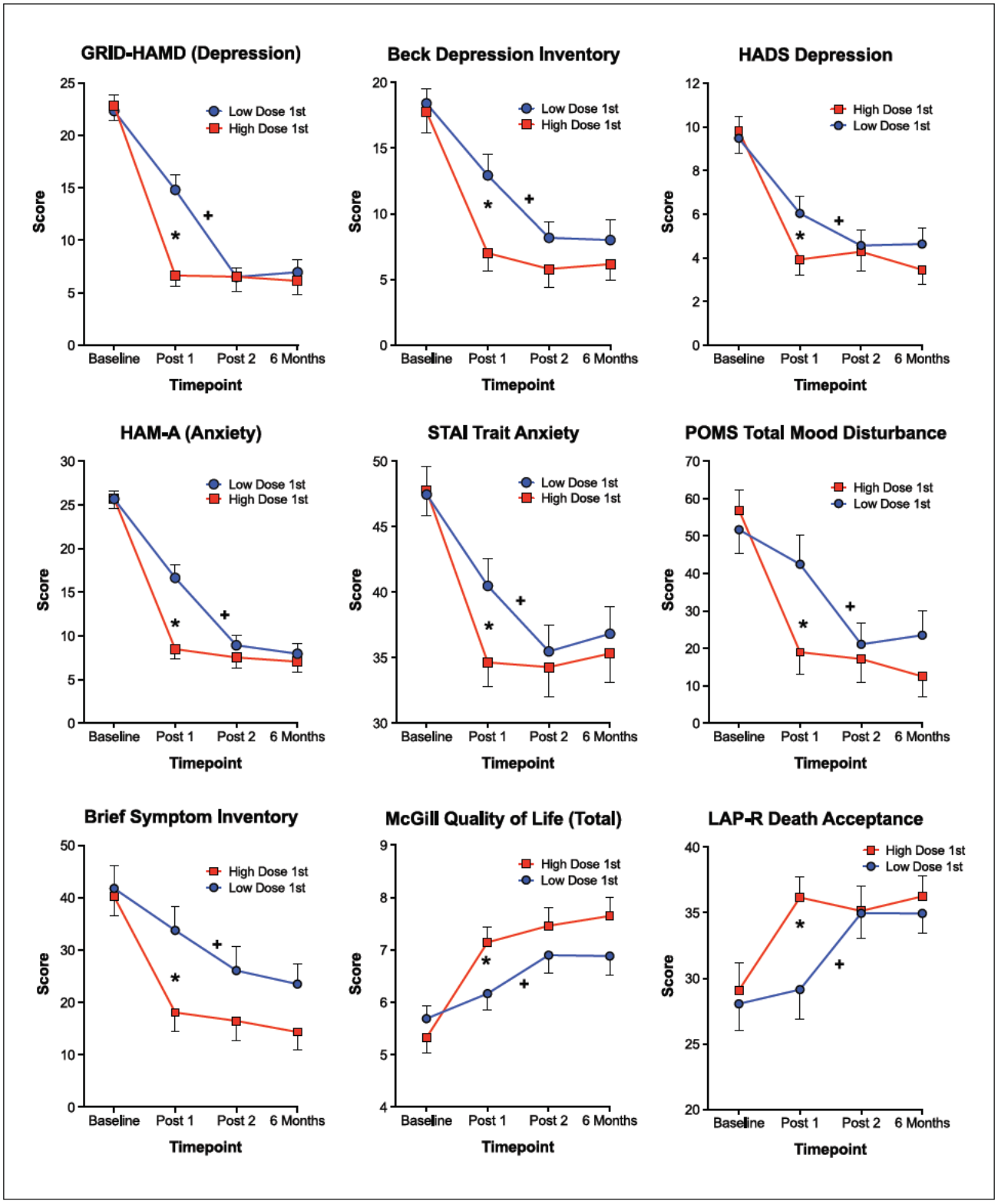

Figure 3. Effects of psilocybin on selected outcome measures that were assessed at Baseline, Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6-month follow-up.

Data points show means; brackets indicate 1 SEM; circles represent the group that received a low dose on the 1st session and a high dose on the 2nd session (n = 25, 25, 24, and 22 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively); squares represent the group that received a high dose on 1st session and a low dose on the 2nd session (n = 26, 26, 25, and 24 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively). Star symbol indicates a significant difference between the two groups at the Post-session 1 time-point (p<0.05, planned comparison). Cross symbol indicates a significant difference between the Post-session 1 and Post-session 2 time-points in the Low-Dose-1st (High-Dose-2nd) Group (p<0.05, planned comparison).

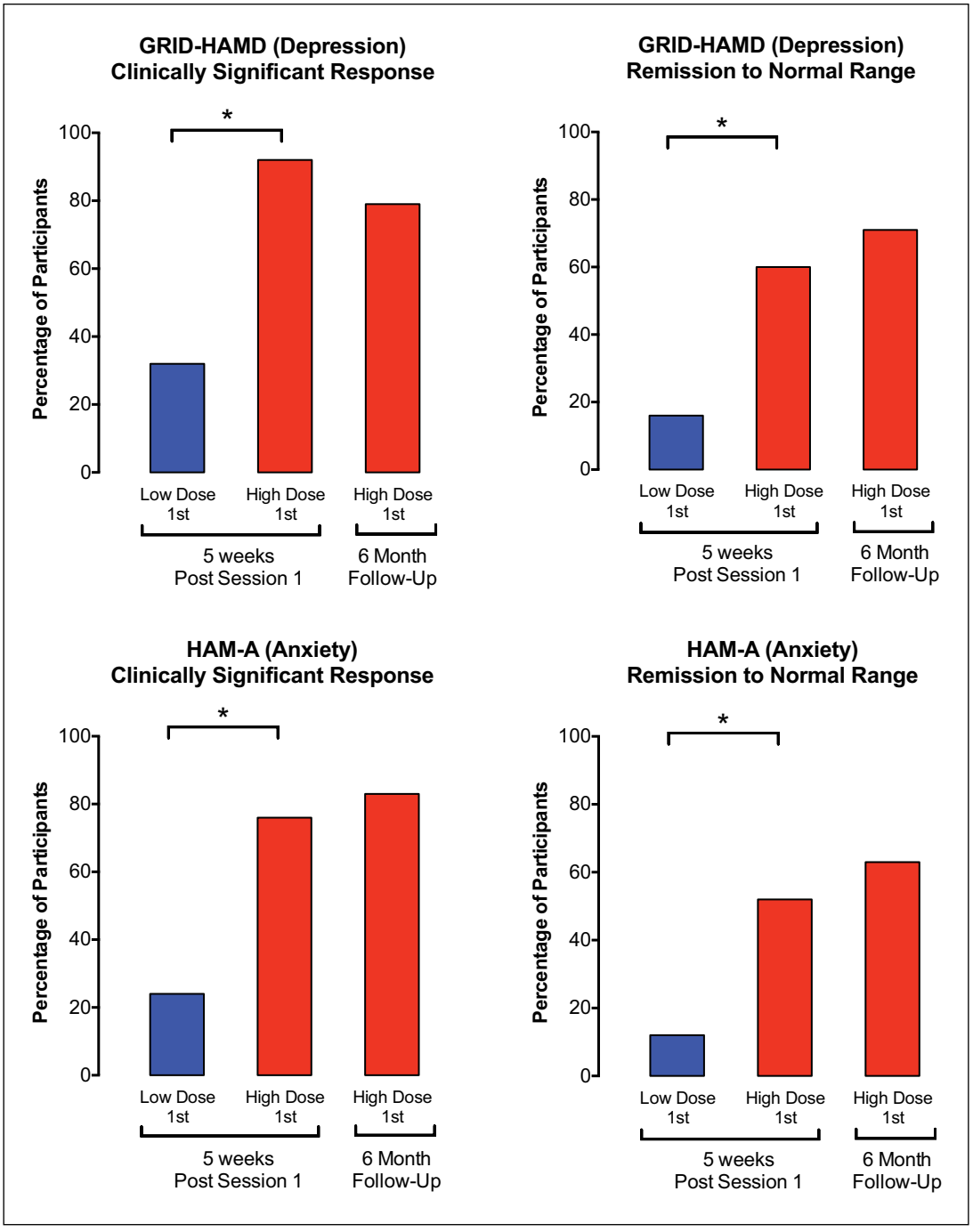

Figure 4. Effects of psilocybin on clinically significant response rate and symptom remission rate as assessed with clinician-rated measures of depression and anxiety.
Data are percentage of participants fulfilling criteria at Post-session 1 (5 weeks after Session 1) and at 6 months. Asterisks indicates that the low and high-dose groups were significantly different at 5 weeks (p>0.001); data at 6 months show these effects were sustained at follow-up. See Table 6 for other details.

changes in the expected directions at Post-session 2 that were generally sustained at the 6-month follow-up.

Table 8 shows participant ratings of persisting effects attributed to the session experiences rated 5 weeks after the low- and high-dose psilocybin sessions, and, again, for the high-dose session at the 6-month follow-up. The high dose produced significantly greater ratings of positive persisting effects on attitudes about life and self, mood changes, social effects, behavior, and spirituality. These effects were sustained at 6-month follow-up. Negative ratings of these dimensions were low and not significantly different between conditions. The high-dose experiences were rated as producing significantly greater personal meaning, spiritual significance and increased well-being or life satisfaction, with differences sustained at 6 months.

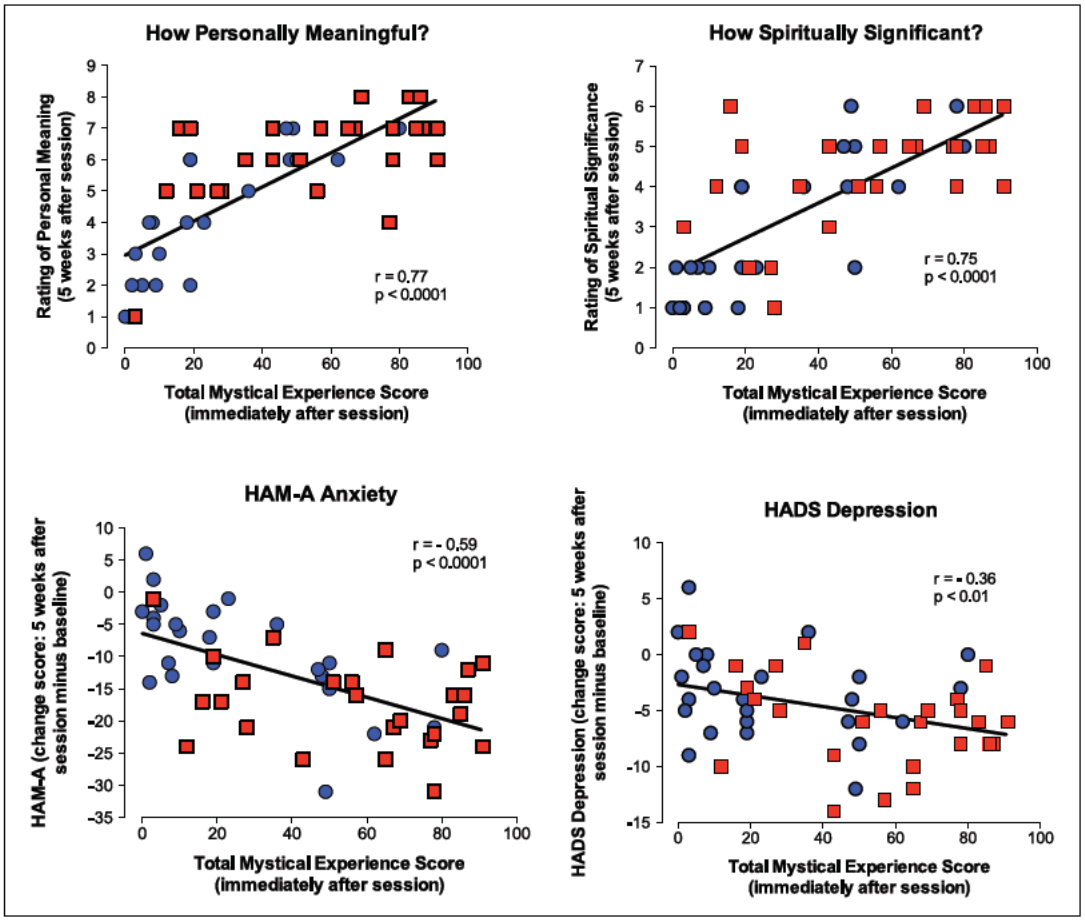

Figure 5. Relationship between the Mystical Experience Questionnaire (MEQ30) total score assessed at end of Session 1 and several illustrative outcome measures assessed 5 weeks after Session 1.

Each panel shows scores on an outcome measure assessed 5 weeks after Session 1 as a function of the total MEQ30 score obtained 7 h after psilocybin administration on Session 1. MEQ30 scores are expressed as a percentage of maximum possible score. Data points represent individual participants (n = 50 or 51); blue circles represent the group that received the low dose on the 1st session; red squares represent the group that received the high dose on the 1st session. Correlation coefficients and p-values are shown.

Mystical experience scores (MEQ30) assessed at the end of Session 1 correlated significantly with 18 of 20 measures assessed 5 weeks after the session: ratings of meaningfulness (r = 0.77), spiritual significance (r = 0.75), increased life satisfaction (r = 0.53), GRID-HAMD (r = −0.41), BDI (r = −0.30), HADS Depression (r = −0.36), HADS Total (r = −0.41), HADS Anxiety (r = −0.34), HAM-A (r = −0.59), STAI-Trait Anxiety (r = −0.31), POMS Total Mood Disturbance (r = −0.35) BSI (r = −0.38), MQOL (r = 0.32), MQOF-meaningful existence (r = 0.41), LAP-R Death Acceptance (r = 0.38), Death Transcendence Scale (r = 0.31), Purpose in Life (r = 0.29), LAP-R Coherence (r = 0.41). Figure 5 shows some of these effects. To further examine the contribution of mystical experience to these outcome measures, partial correlations were conducted to control for the participant-rated intensity of drug effect, which, like mystical experience, was assessed at the end of the session. This analysis continued to show significant effects of mystical experience on 11 of these 18 measures (meaningfulness, spiritual significance, life satisfaction, GRID-HAMD, HADS Depression, HADS Total, HADS Anxiety, HAM-A, BSI, MQOL-meaningful existence and LAP-R Coherence). Finally, a mediation analysis showed that MEQ30 score was a significant mediator of the effect of psilocybin dose on seven of these outcome measures. Point estimates and bias-corrected 95% confidence intervals for the indirect effects of the mediation analysis were: meaningfulness (1.43 [0.72–2.44]), spiritual significance (1.19 [0.59–2.10]), life satisfaction (0.60 [0.218–1.19]), HADS Anxiety (−1.50 [−3.50 to −0.33]), HADS Depression (−1.11 [−2.79 to −0.02]), HADS Total (−2.62 [−5.74 to −0.72]), and HAM-A (−3.93 [−7.88 to −1.52]).

Discussion

The present study demonstrated the efficacy of a high dose of psilocybin administered under supportive conditions to decrease symptoms of depressed mood and anxiety, and to increase quality of life in patients with a life-threatening cancer diagnosis. Eleven of 17 therapeutically relevant measures fulfilled conservative criteria for demonstrating efficacy of the high dose of psilocybin (Table 4, Figure 3). The data show that psilocybin produced large and significant decreases in clinician-rated and self-rated measures of depression, anxiety or mood disturbance, and increases in

measures of quality of life, life meaning, death acceptance, and optimism. These effects were sustained at 6 months. For the clinician-rated measures of depression and anxiety, respectively, the overall rate of clinical response at 6 months was 78% and 83% and the overall rate of symptom remission was 65% and 57%. Participants attributed to the high-dose experience positive changes in attitudes about life, self, mood, relationships and spirituality, with over 80% endorsing moderately or higher increased well-being or life satisfaction. These positive effects were reflected in significant corresponding changes in ratings by community observers (friends, family, work colleagues) of participant attitudes and behavior.

The results substantially extend the findings of a recent double-blind pilot study with a lower dose of psilocybin (14 mg/70 kg) in cancer patients that showed non-significant trends for benefits of psilocybin compared with placebo (niacin) on measures of depression and anxiety, with some significant decreases relative to baseline demonstrated at 1 to 6 months (Grob et al., 2011).

The time-course, magnitude, and qualitative features of the high dose of psilocybin on session days were consistent with those observed in previous studies in healthy volunteers (Griffiths et al., 2006, 2011; Johnson et al., 2012).

The significant association of mystical-type experience (MEQ30) during Session 1 with most of the enduring changes in therapeutic outcome measures 5 weeks later (Figure 5) is consistent with previous findings showing that such experiences on session days predict long-term positive changes in attitudes, mood, behavior, and spirituality (Garcia-Romeu et al., 2014; Griffiths et al., 2008, 2011). For most measures, this relationship continued to be significant when the intensity of overall psilocybin effect was controlled in a partial correlation analysis. This suggests that mystical-type experience per se has an important role apart from overall intensity of drug effect. Finally, a mediation analysis further suggested that mystical-type experience has a mediating role in positive therapeutic response.

The observed decreases in psychological distress and anxiety about death may relate to recent epidemiological findings that lifetime psilocybin use was associated with significantly reduced odds of past month psychological distress and suicidality (Hendricks et al., 2015).

An innovative feature of the study design was that participants and staff monitors were given instructions that obscured the actual psilocybin dose conditions to facilitate blinding and minimize expectancy effects, which are believed to be a significant determinant of classic hallucinogen effects (Griffiths et al., 2006; Metzner et al., 1965). Evidence of some success of this blinding was provided in a post-study questionnaire completed by staff and by significant treatment effects observed after Session 1 in participants who received the very low dose of psilocybin. Although it was assumed that 1 mg/70 kg would be largely pharmacologically inactive, some pharmacological activity of this dose cannot be ruled out entirely. Thus, it might have been preferable to use an even lower dose of psilocybin (e.g. 0.01 mg/70 kg) to assure pharmacological inactivity while maintaining the benefit of the instruction that psilocybin would be administered on each session. Although the low-dose comparison condition and instructions to participants and staff facilitated blinding and minimized expectancy effects, it should be noted that these experimental design features may be difficult to implement in research settings that require complete disclosure of specific study conditions or arms.

Several additional experimental limitations should be noted. Participants were crossed over to the alternative dose condition after 5 weeks. Although this allowed assessment of acute and persisting effects of psilocybin in all study participants, it precluded double-blind assessment of efficacy of the high dose of psilocybin based on across group comparisons after 5 weeks. As in previous research, the study documented enduring increases in positive changes in attitudes and mood on both the participant-rated Persisting Effects Questionnaire and on the Community Observer Questionnaire (Griffiths et al., 2006, 2011). However, neither of these measures has been independently validated. Likewise, although the finding of significant decreases in depression and anxiety symptoms on both participant-rated and clinician-rated measures is a strength, the inclusion of blinded clinician ratings would further strengthen the study. The relatively small sample (n = 51) that was highly educated and predominately White limits the generality of conclusions.

Finally, it is important to note that the overall approach of treating cancer-related psychological distress with psilocybin is limited by a variety of exclusion criteria (see online Supplementary material) and by the significant time and cost of professional support provided before, during, and after the psilocybin session. Patients may also be reluctant to participate in such an intervention because high doses of psilocybin have sometimes been associated with transient episodes of psychological distress or anxiety in patients (current study and studies in healthy volunteers, Griffiths et al., 2006, 2011).

The neuropsychopharmacological mechanisms of psilocybin therapeutic effects remain speculative (Carhart-Harris et al., 2012, 2014; Nichols, 2016; Vollenweider and Kometer, 2010). As a 5-HT_{2A} agonist, the psilocybin metabolite psilocin directly and indirectly affects various brain cortical and subcortical areas and alters brain network dynamics (Carhart-Harris et al., 2012, 2014; Vollenweider and Kometer, 2010). Precisely how the enduring therapeutically relevant psilocybin effects are reflected in long-term alteration of cortical networks or other neuroplastic changes remains to be established.

Conclusions

When administered under psychologically supportive, double-blind conditions, a single dose of psilocybin produced substantial and enduring decreases in depressed mood and anxiety along with increases in quality of life and decreases in death anxiety in patients with a life-threatening cancer diagnosis. Ratings by patients themselves, clinicians, and community observers suggested these effects endured at least 6 months. The overall rate of clinical response at 6 months on clinician-rated depression and anxiety was 78% and 83%, respectively. A multisite study in a larger and more diverse patient population should be conducted to establish the generality and safety of psilocybin treatment of psychological distress associated with life-threatening cancer.

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Commentary

The role of psychedelics in palliative care reconsidered: A case for psilocybin

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Psychiatric research with classic hallucinogens has enjoyed a resurgence of late. While studies performed in the late 1960s and early 1970s with lysergic acid diethylamide (LSD) and psilocybin demonstrated therapeutic promise by producing a rapid and sustained reduction in anxiety, improvement in mood, and enhanced quality of life in patients with terminal cancer (Grof, 1973), a fuller exploration of their use in palliative medicine was curtailed by the establishment of a strict federal regulatory environment. Now, after decades of research inactivity, the potential of psychedelics to alleviate the distress associated with a terminal illness has been significantly advanced by the results of two recent studies investigating the efficacy of psilocybin in the treatment of anxiety and depression in patients with life-threatening cancer. Using double-blind, placebo-controlled, crossover designs, the studies conducted at Johns Hopkins University (JHU) and New York University (NYU) were methodologically rigorous and broad in the scope of their outcome variables. Both studies demonstrated that a single-dose of psilocybin can produce both an acute and enduring reduction in depression symptoms, anxiety, and existential distress in patients with life-threatening cancer.

That the studies replicated one another is a source of confidence in their findings. However, there were also informative differences between the studies. The group at JHU led by Griffiths et al. investigated the effects of a very low dose (1–3 mg/70 kg, placebo-like) versus high dose (22 mg/70 kg) of psilocybin administered five weeks apart in 51 patients diagnosed with life-threatening cancer and suffering with symptoms of depression and/or anxiety (Griffiths et al., 2016). The group at NYU led by Ross et al. compared the effect of high-dose psilocybin (0.3 mg/kg, ~21 mg/ 70 kg) with niacin (used as an "active" control) in 29 patients, and both groups received targeted psychotherapy (Ross et al., 2016). All patients were screened and prepared for the study intervention through several meetings with staff who established rapport and provided an understanding of the range of altered states of consciousness that might be encountered during their treatment sessions. The psilocybin experience was well tolerated by all patients, and there were no serious medical or psychological adverse events.

Both studies evaluated a broad range of outcome measures, including the common measures of anxiety and depression, as well as quality of life, spirituality, and mystical experiences. In the Griffiths et al. trial, high-dose psilocybin produced large and sustained decreases in clinician- and patient-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning and optimism, and decreases in anxiety related to death. In the NYU trial, psilocybin produced rapid, substantial, and enduring reductions in cancer-related anxiety and depression, improved quality of life, increased spiritual well-being, and improved measures of existential distress, and was associated with improved attitudes toward death. At follow-up at six-and-a-half months, the initial robust clinical effects observed after the administration of a single dose of psilocybin endured in 60–80% of the patients, and when patients were asked (six-and-a-half months post drug administration) to reflect on what they thought of their psilocybin session, 52% and 70% rated the psilocybin experience as the singular or top 5 most spiritually significant, or the singular or top 5 most personally meaningful experience of their entire lives, respectively, while 87% reported increased life-satisfaction or well-being attributed to the experience (Ross et al., 2016). The findings that single-dose psilocybin can produce acute and sustained improvements in cancer-related anxiety and depression is perhaps the most important and novel finding of the two studies, and add to and extend the findings of a similarly designed trial in patients with terminal cancer where a single low dose (0.2 mg/kg) of psilocybin showed non-significant trends for benefit compared with placebo (Grob et al., 2011).

In both studies, mediation analysis indicates that the mystical experience was a significant mediator of the effects of psilocybin dose on therapeutic outcomes. Mystical experience is defined as encountering a profound sense of unity, transcendence of time and space, deeply felt positive mood, noetic quality (sense of understanding), ineffability, transiency, and paradoxicality infused with a renewed sense of purpose and meaning (Griffiths, 2006, 2008, 2011; Grob et al., 2013). Further evidence for the

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role of the mystical experience and/or higher doses in therapeutic outcomes comes from two open-label trials for addiction where the mystical experience was correlated with improved smoking cessation (Garcia-Romeu et al., 2014) and drinking outcomes (Bogenschutz et al., 2015). Furthermore, Carhart-Harris et al. (2016) recently investigated the safety and efficacy of psilocybin in treatment-resistant depression, and showed that a higher dose correlated with a better treatment outcome. The association between psychedelic-induced mystical experience and therapeutic outcome, while not new, requires further exploration, as when induced under optimal conditions and in a controlled setting, it could provide a valuable therapeutic intervention for disorders that are otherwise difficult to treat.

Although not the primary aim of these studies, directionality of the relationship between the pharmacology of the drug, mystical experiences, and clinical outcome remains inconclusive. We do not know for certain whether these mystical experiences are a cause, consequence or corollary of the anxiolytic effect or unconstrained cognition (see below). For instance, it is possible that mystical experiences associated with psilocybin serve as a measure of adequate drug effects rather than mediating an antidepressant and/or anxiolytic effect. Perhaps future studies could shed some light on this relationship by employing other drugs, such Salvinorin A and other kappa opioid receptor agonists, capable of producing perceptual alterations and mystical experiences similar to serotonergic hallucinogens but pharmacologically different (Johnson et al., 2011; Ranganathan et al., 2012). Also intriguing is whether the psychoactive effects of psilocybin influence its efficacy through, not yet fully understood, psychological mechanisms that continue to exert their effect well beyond the acute pharmacological effects. Rapid alleviation in mood is also reported with a single administration of ketamine, a dissociative anesthetic known to occasion mystical experiences. However, the antidepressant effects are relatively transient and typically disappear after a week. Moreover, not all the psychotropic substances (e.g., scopolamine and nitrous oxide) that induce dissociative and/or mystical experiences produce an acute and enduring clinical benefit. Is there a differentially unique characteristic about the pharmacology of psilocybin and its enduring clinical effects compared with other serotonin receptor (5-HT2A) agonists such as dimethyltryptamine or dipropyltryptamine?

Imaging studies in healthy controls indicate that psilocybin decreases blood flow to regions of the brain regions collectively known as the default mode network (DMN) and promotes unconstrained cognition (Carhart-Harris et al., 2012, 2014). Increase in metabolic activity in the DMN has been associated with increase in ruminative thinking and has been implicated in depression and anxiety but normalized by a range of effective treatments (Carhart-Harris et al., 2014). One theoretical framework that might link mystical experiences to a new, more positive outlook through changes in brain function is Predictive Processing (Friston, 2005). This theory posits that the brain is a prediction machine and its hierarchically organized neuroanatomy is geared toward predicting future inputs based on prior experiences. Any mismatches or prediction errors (coded glutamatergically) can gather new learning based in their precision (implemented by slower neuromodulators such as dopamine, acetylcholine, or serotonin, depending on the inferential hierarchy) Corlett et al., 2009). We have previously argued that psychotomimetic drugs may induce their psychedelic or mystical effects by altering the balance between predictions and prediction errors such that errors are registered inappropriately and perceptual inferences become deranged (Corlett et al., 2009). These experiences can gather new learning, expanding the possibility space for future inferences (Corlett et al., 2010). This may be reflected in the significantly elevated trait openness, which persists for 14 months following a single infusion of psilocybin (MacLean et al., 2011). Future work will need to discern how and why these drugs can have psychotomimetic effects in some individuals and antidepressant effects in others. The environmental setting and individual's baseline are clearly crucial to the effects a psychedelic drug can have (Zinberg, 1984). Thus expectations and environments may enhance the drug's potential to foster religious and spiritual experiences. In his book *Heaven and Hell*, Aldous Huxley observes, "Many schizophrenics have their times of heavenly happiness; but the fact that (unlike the mescaline taker) they do not know when, if ever, they will return to the reassuring banality of everyday experiences causes even heaven to seem appalling."

These studies have demonstrated a critical advancement in this field. Psilocybin may offer a novel and potentially valuable approach for addressing the psychological suffering of dying often observed in this patient population, particularly given the limited efficacy of extant treatments. These studies also raise a number of important questions that warrant further research. How necessary are the acute psychedelic effects of psilocybin for its antidepressant and anxiolytic effects? What are the predictors of beneficial effects and adverse effects? Would moderate doses have similar effects? How specific are the effects? For a single dose of a drug to have effects that are still detectable six months later opens a new era of potential psychopharmacological treatments. But it also begs the question about what is/are the mechanism/s underlying the sustained beneficial clinical effects of psilocybin.

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Original Paper

Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial

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Abstract

Background: Clinically significant anxiety and depression are common in patients with cancer, and are associated with poor psychiatric and medical outcomes. Historical and recent research suggests a role for psilocybin to treat cancer-related anxiety and depression.

Methods: In this double-blind, placebo-controlled, crossover trial, 29 patients with cancer-related anxiety and depression were randomly assigned and received treatment with single-dose psilocybin (0.3 mg/kg) or niacin, both in conjunction with psychotherapy. The primary outcomes were anxiety and depression assessed between groups prior to the crossover at 7 weeks.

Results: Prior to the crossover, psilocybin produced immediate, substantial, and sustained improvements in anxiety and depression and led to decreases in cancer-related demoralization and hopelessness, improved spiritual wellbeing, and increased quality of life. At the 6.5-month follow-up, psilocybin was associated with enduring anxiolytic and anti-depressant effects (approximately 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. The psilocybin-induced mystical experience mediated the therapeutic effect of psilocybin on anxiety and depression.

Conclusions: In conjunction with psychotherapy, single moderate-dose psilocybin produced rapid, robust and enduring anxiolytic and anti-depressant effects in patients with cancer-related psychological distress.

Trial Registration: ClinicalTrials.gov Identifier: NCT00957359

Keywords

Psilocybin, psychedelic, cancer, depression, anxiety, mystical experience

Introduction

Enduring clinically significant anxiety and/or depressive symptoms are common in patients with cancer, present in 30–40% of patients in hospital settings (Mitchell et al., 2011). These symptoms are associated with a variety of poor outcomes, including medication non-adherence, increased health care utilization, adverse medical outcomes, decreased quality of life, decreased social function, increased disability, hopelessness, increased pain, increased desire for hastened death, increased rates of suicide, and decreased survival rates (Arrieta et al., 2013; Brown et al., 2003; Jaiswal et al., 2014).

Although pharmacotherapeutic and psychosocial interventions are commonly used to treat anxiety and depression in cancer patients, their efficacy is mixed and limited (Grassi et al., 2014; NCCN, 2014). There are no US Food and Drug Administration approved pharmacotherapies for cancer-related psychological distress, the onset of clinical improvement with anti-depressants is delayed, relapse rates are high, and significant side effects compromise treatment adherence (Freedman, 2010; Li et al., 2012).

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With a growing body of evidence linking higher levels of existential/spiritual wellbeing (in cancer patients) with improved quality of life and decreased depression/hopelessness/suicidality (Breitbart et al., 2000; McClain et al., 2003; Nelson et al., 2002), the need to develop effective therapeutic approaches to mitigate this domain of distress has become increasingly recognized within the disciplines of palliative care and psycho-oncology (emphasized within the last two decades by the Institute of Medicine, the World Health Organization, the National Comprehensive Cancer Network, the Joint Commission, the National Consensus Project, and the National Quality Forum) and improvement in these domains is now accepted as an integral component in the care of cancer patients (Puchalski, 2012). A number of manualized existentially oriented psychotherapies have been developed to address these existential/spiritual issues, with some empirical support from clinical trials (Lemay and Wilson, 2008), and several of these approaches were integrated into the therapy platform developed for this study. There are currently no pharmacotherapies or evidence-based combined pharmacological-psychosocial interventions to treat this particular type of distress and unmet clinical need in cancer patients (Breitbart et al., 2010).

Psilocybin, a tryptamine serotoninergic psychedelic, exerts its consciousness altering effects via 5HT2A agonism (Vollenweider and Kometer, 2010). It has a well-established physiological and psychological safety profile in human laboratory and clinical trial research (Johnson et al., 2008), is not known to be addictive and may have anti-addictive properties (Bogenschutz and Johnson, 2016; Krebs and Johansen, 2012; Ross, 2012). It can produce highly salient spiritual/mystical states of consciousness associated with enduring (months to years) positive changes in cognition, affect, behavior, and spirituality (Doblin, 1991; Griffiths et al., 2006, 2008, 2011; Pahnke, 1963). From the early 1960s to the early 1970s, clinical research utilizing the serotoninergic psychedelics, primarily lysergic acid diethylamide (LSD), to treat terminal cancer-related psychological and existential distress was conducted at major academic medical centers in the United States with a total of several hundred participants. These studies occurred largely in the context of open-label trials and showed improvements in the following symptom domains: anxiety, depression, fear of dying, quality of life, and pain (Grob et al., 2013; Grof et al., 1973; Kast, 1966; Kast and Collins, 1964; Pahnke et al., 1969).

Research into the use of hallucinogen treatment models for psycho-spiritual distress in advanced or terminal cancer ceased in the mid 1970s with the passage of the Controlled Substance Act of 1970, which placed all of the serotoninergic psychedelics into schedule I of the US Drug Enforcement Administration's classification of regulated psychoactive substances.

Building upon hallucinogen research with cancer patients from over four decades ago, two recently published randomized controlled trials (RCTs) with serotoninergic psychedelics to treat cancer-related psychological distress, one using psilocybin in patients with advanced-stage cancer conducted at Harbor-UCLA (Grob et al., 2011) and the other using LSD in patients with a variety of life-threatening illnesses including but not limited to cancer diagnoses (Gasser et al., 2014), suggested acute and sustained treatment benefits. The University of California Los Angeles RCT in patients with advanced-stage cancer included a cohort of 12 participants and reported on the medical and psychiatric safety of administering low-dose psilocybin (0.2 mg/kg) in conjunction with psychotherapy, and revealed trends towards reduced depression and anxiety in the psilocybin group compared to the control condition (Grob et al., 2011).

In the present RCT, the primary hypothesis was that psilocybin, in conjunction with targeted psychotherapy, would significantly decrease anxiety and depression symptoms (compared to an active control, niacin, and the same dose of psychotherapy as the experimental group) in patients with life-threatening cancer diagnoses.

Methods

Study design and interventions

This randomized, blinded, controlled, crossover, study was designed to investigate the efficacy of a single psilocybin dosing session (0.3 mg/kg) versus one dosing session of an active control (niacin 250 mg), administered in conjunction with psychotherapy, to treat clinically significant anxiety or depression in patients with life-threatening cancer (see Supplementary Methods for information on inclusion/exclusion criteria, blinding procedures, medication sessions and psychotherapy procedures). The trial employed a two-session, double-blind, crossover (7 weeks after administration of dose 1) design to compare groups. Participants were randomly assigned to two oral dosing session sequences: psilocybin (0.3 mg/kg) first then niacin (250 mg) second, or niacin (250 mg) first then psilocybin (0.3 mg/kg) second (Figures 1 and 2). Randomization did not stratify for any demographic (i.e. gender, race, spiritual/religious affiliation) or clinical characteristics (i.e. stage of cancer, prior hallucinogen use). Drug administration dose 1 (psilocybin or control) occurred 2–4 weeks (mean 18 days) after baseline assessments and the crossover occurred 7 weeks (mean 52 days) after dose 1, at which point drug administration dose 2 occurred. Data assessments occurred at baseline (2–4 weeks prior to dose 1), 1 day prior to dose 1, day of dose 1 (7 hours post-dose), 1 day after dose 1, 2 weeks after dose 1, 6 weeks after dose 1, 7 weeks after dose 1 (1 day prior to dose 2), day of dose 2 (7 hours post-dose), 1 day after dose 2, 6 weeks after dose 2, and 26 weeks after dose 2 (Figure 2). The total duration of study participation was approximately 9 months (mean 253 days). The primary outcome variables were anxiety and depression assessed prior to the crossover. Secondary outcome measures (assessed before and after the crossover) included assessments of existential distress, quality of life, and spirituality, as well as measures assessing immediate and sustained effects of psilocybin administration on subjective (e.g. mystical) experience, cognition, affect, spirituality, and behavior.

Study sample and setting

Of 108 participants pre-screened, 42 gave informed consent and of these 29 patients were randomly assigned and received treatment with single-dose psilocybin or single-dose niacin control (Table 1 and Figure 1). The study was approved and monitored by the institutional review board of the New York University (NYU) School of Medicine. The majority of participants were recruited from a clinical cancer center at an academic medical facility (NYU Langone's Perlmutter Cancer Center). Data were collected from 18 February 2009 to 22

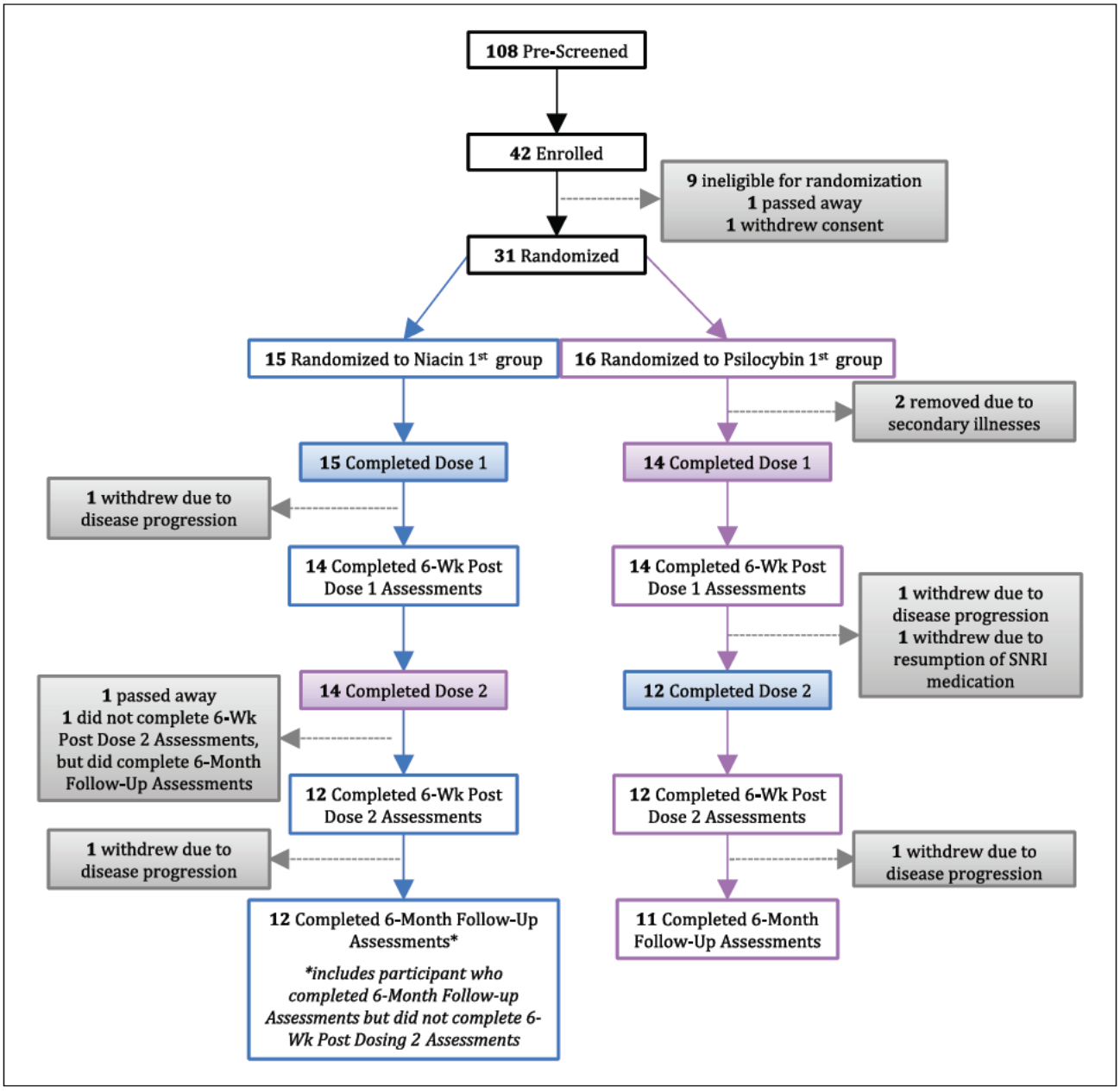


Figure 1. CONSORT diagram.

October 2014 and the analysis was conducted from 3 November 2014 to 11 December 2015.

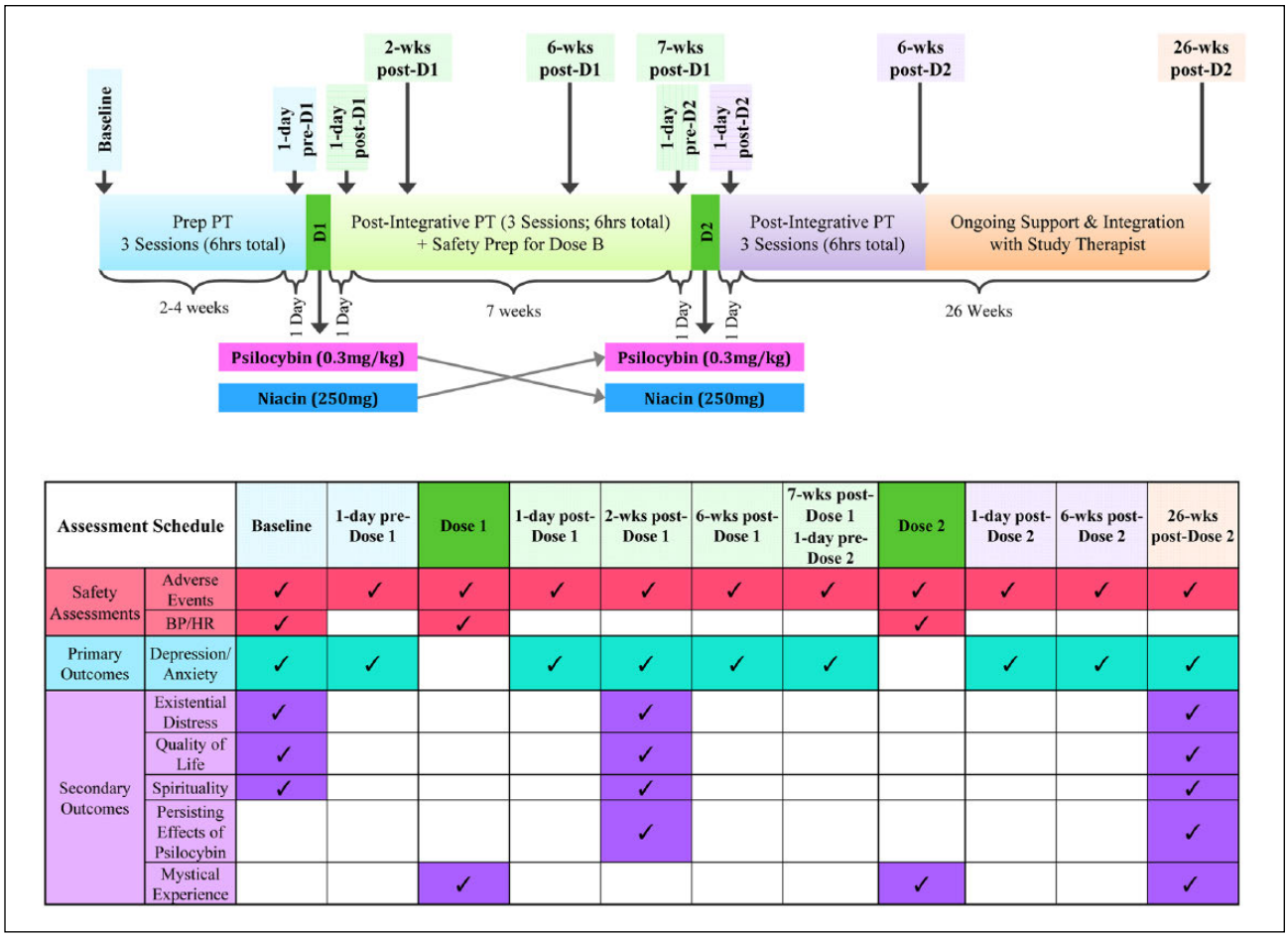
Nearly two-thirds of participants (62%) had advanced cancers (stages III or IV). The types of cancer included: breast or reproductive (59%); gastrointestinal (17%); hematologic (14%); other (10%). In accordance with the study's inclusion criteria, all participants carried an anxiety-related diagnosis per the severe combined immunodeficiency (SCID) (Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV) with the majority meeting criteria for an adjustment disorder (26, 90%) and the rest for generalized anxiety disorder (three, 10%). Nearly two-thirds (59%) had previously been treated with anti-depressant or anxiolytic medication, but none were on any psychotropics at the time of study enrollment, per the inclusion/exclusion criteria.

Assessments

Safety assessments. Adverse events (AEs) attributed to study medications (psilocybin, niacin) were monitored throughout the trial, including during and after medication administration sessions.

Cardiovascular measures were assessed during medication sessions. Systolic and diastolic blood pressure (BP) and heart rate (HR) were measured at the following time points during the medication dosing sessions: baseline, 30, 60, 90, 120, 180, 240, 300, 360 minutes post-dose administration.

Primary Outcome Measures. Clinical primary outcome measures (anxiety, depression) were assessed at baseline, 1 day prior



Assessment Schedule		Baseline	1-day pre-Dose 1	Dose 1	1-day post-Dose 1	2-wks post-Dose 1	6-wks post-Dose 1	7-wks post-Dose 1 1-day pre-Dose 2	Dose 2	1-day post-Dose 2	6-wks post-Dose 2	26-wks post-Dose 2
Safety Assessments	Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	BP/HR	✓		✓					✓			
Primary Outcomes	Depression/ Anxiety	✓	✓		✓	✓	✓	✓		✓	✓	✓
Secondary Outcomes	Existential Distress	✓				✓						✓
	Quality of Life	✓				✓						✓
	Spirituality	✓				✓						✓
	Persisting Effects of Psilocybin					✓						✓
	Mystical Experience			✓					✓			✓

Figure 2. Interventions and assessments schedule.
Temporal relationships between drug administration, psychosocial interventions, and assessments.
Prep PT: preparatory psychotherapy; 1-day pre-D1: 1 day prior to dose 1; Dose 1: dosing session 1; 1-day post-D1: 1 day after dose 1; Post-integrative PT: post-integrative psychotherapy; 2-wks post-D1: 2 weeks after dose 1; 6-wks post-D1: 6 weeks after dose 1; Safety prep for D2: safety preparation for dosing dose 2; 1-day pre-D2: 1 day prior to dose 2; Dose 2: dosing session 2; 1-day post-D2: 1 day after dose 2; 6-wks post-D2: 6 weeks after dose 2; 26-wks post-D2: 2 weeks after dose 2.

to dose 1, 1 day after dose 1, 2-weeks after dose 1, 6 weeks after dose 1, 7 weeks after dose 1 (corresponding to 1 day prior to dose 2), 1 day after dose 2, 6 weeks after dose 2, and 26 weeks after dose 2: Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), self-rated subscales of anxiety (HADS anxiety or HAD A), depression (HADS depression or HAD D) and total (HADS total or HAD T) combined score in patients with physical health problems (e.g. cancer); Beck Depression Inventory (BDI) (Beck et al., 1988) self-report depression measure; Spielberger State-Trait Anxiety Inventory (STAI) (Spielberger, 1983) self-report measure of state (STAI state or STAI S) and trait (STAI trait or STAI T) anxiety.

Secondary outcome measures. Cancer-related existential distress (demoralization, hopelessness, attitudes and affect associated with disease progression and death) was assessed at baseline, 2 weeks post-dose 1, and 26 weeks post-dose 2: Demoralization (DEM) scale (Kissane et al., 2004), self-report measure of the cancer-related demoralization syndrome (e.g. despair, helplessness, existential distress such as loss of hope/meaning/purpose in life, a sense of 'giving up', desire for hastened death); Hopelessness Assessment and Illness (HAI) scale (Rosenfeld et al., 2011) self-report measure of hopelessness in advanced cancer; Death Anxiety Scale (DAS) (Templer, 1970) a self-report questionnaire assessing the level of death anxiety; Death Transcendence Scale (DTS) (VandeCreek, 1999) a self-report measure of positive attitudes and adaptations to the finitude of life.

Quality of life was assessed at baseline, 2 weeks post-dose 1 and 26 weeks post-dose 2: World Health Organization Qualify of Life scale, brief version (WHO-Bref) (WHO, 1994), self-report measure of quality of life in four domains (physical, psychological, social relationships, environment).

Spirituality was assessed at baseline, 2 weeks post-dose 1 and 26 weeks post-dose 2: Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-SWB) (Brady et al., 1999) a self-report measure of spiritual wellbeing generating three scales: meaning/peace, faith, total spiritual wellbeing score. The meaning/peace scale assesses one's sense of inner peace, meaning, and purpose in life and corresponds to the more existential components of religious or spiritual practice. The faith scale measures strength and comfort derived from one's faith and emphasizes the more ritualized components of religious/spiritual practice.

Table 1. Demographic and clinical characteristics of study participants.[a]

Characteristic	Categories	Psilocybin first		Niacin first		Total	
		n=14		*n*=15		*n*=29	
Sex	Female	7	50%	11	73%	18	62%
	Male	7	50%	4	27%	11	38%
Age; mean (SD)	Range 22–75	52 (15.03)		60.27 (9.45)		56.28 (12.93)	
Race	White/Caucasian	13	93%	13	87%	26	90%
	Black/African American	0	0%	0	0%	0	0%
	Hispanic/Latino	0	0%	0	0%	0	0%
	Asian	0	0%	0	0%	0	0%
	American Indian/Native American	0	0%	0	0%	0	0%
	Other	1	7%	2	13%	3	10%
Religious/ spiritual beliefs	Atheist/agnostic	4	29%	10	67%	14	48%
	Jewish	4	29%	1	7%	5	17%
	Catholic	2	14%	0	0%	2	7%
	Other Christian	3	21%	1	7%	4	14%
	Other faith/tradition	1	7%	3	20%	4	14%
Site of cancer	Breast	4	29%	5	33%	9	31%
	Reproductive	3	21%	5	33%	8	28%
	Digestive cancers	3	21%	2	13%	5	17%
	Lymphoma/leukemia	2	14%	2	13%	4	14%
	Other types	2	14%	1	7%	3	10%
Stage of cancer	Stage IV	3	21%	7	47%	10	34%
	Stage III	4	29%	4	27%	8	28%
	Stage II	1	7%	4	27%	5	17%
	Stage I	5	36%	0	0%	5	17%
	Other	1	7%	0	0%	1	3%
SCID (DSM-IV) diagnosis[b]	Adjustment disorder w/anxiety and depressed mood, chronic	2	14%	6	40%	8	28%
	Adjustment disorder w/anxiety, chronic	10	71%	8	53%	18	62%
	Generalized anxiety disorder	2	14%	1	7%	3	10%
Hallucinogen use	No	7	50%	6	40%	13	45%
	Yes	7	50%	9	60%	16	55%
Employment status	Full-time employed	6	43%	5	33%	12	41%
	Part-time employed	2	14%	2	13%	4	14%
	Full-time student	1	7%	0	0%	1	3%
	Unemployed	2	14%	1	7%	2	7%
	Self-employed	1	7%	1	7%	2	7%
	Retired	0	0%	6	40%	6	21%
	Long-term disability	2	14%	0	0%	2	7%
Educational attainment	Grade 7–12 w/o graduating high school	1	7%	0	0%	1	3%
	Graduated HS or equivalent	0	0%	1	7%	1	3%
	Part college	1	7%	3	20%	4	14%
	Graduated 4-year college	5	36%	4	27%	9	31%
	Completed grad/professional school	7	50%	7	47%	14	48%
Marital status	Never married	5	36%	3	20%	8	28%
	Widowed	0	0%	2	13%	2	7%
	Cohabitation	2	14%	0	0%	2	7%
	Divorced	1	7%	3	20%	4	14%
	Married	6	43%	7	47%	13	45%
Living arrangements	Live with spouse/partner/family	11	79%	9	60%	20	69%
	Live alone	2	14%	6	40%	8	28%
	Other; lived with roommates	1	7%	0	0%	1	3%

[a]The two dose-sequence groups did not significantly differ on any demographic or clinical characteristic measures.
[b]Psychiatric classification was based on the structured clinical interview for the DSM-IV (SCID-IV).
Nearly two-thirds (59%) of participants had previously been treated with anti-depressant or anxiolytic medication, but none were on any psychotropics before study enrollment per inclusion/exclusion criteria.

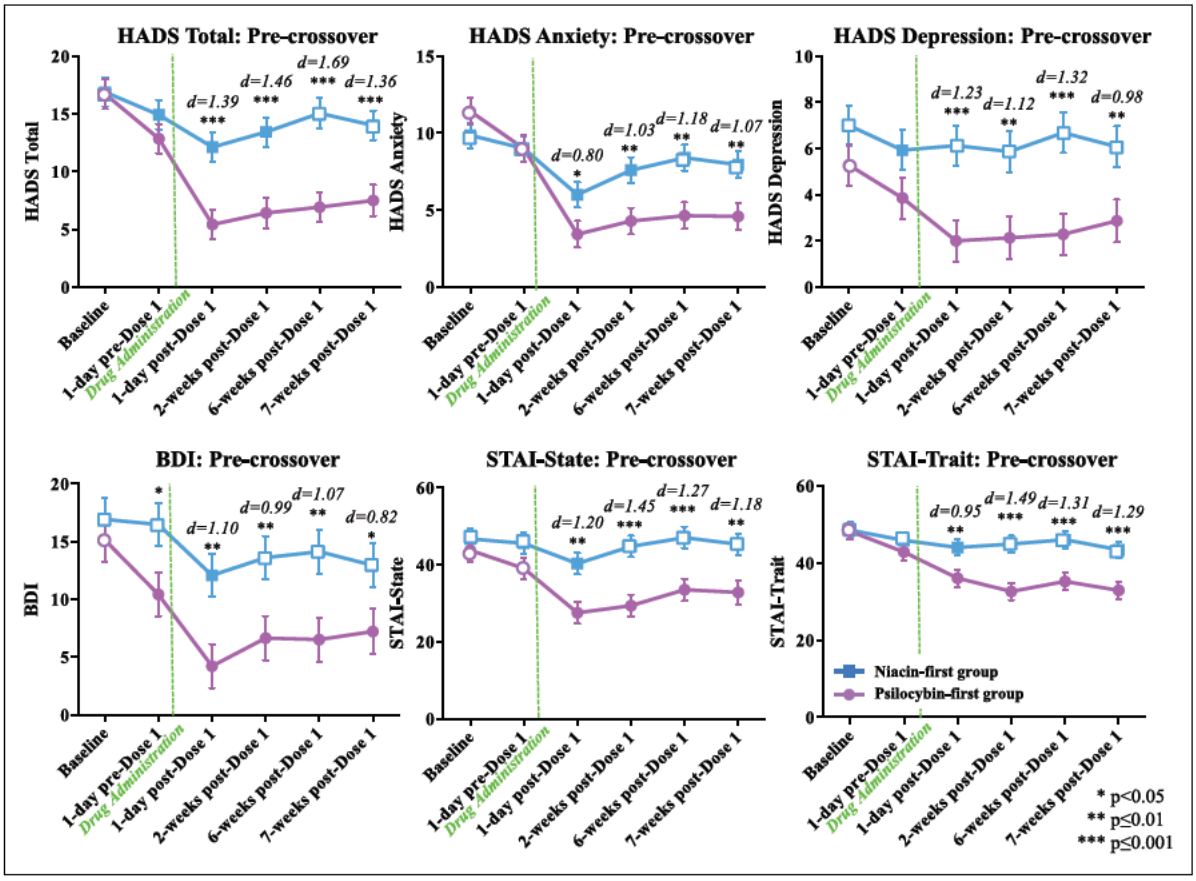


Figure 3. Primary outcome variables: cancer-related anxiety and depression (pre-crossover).
Means (±SE) for primary outcome measures are shown in the two treatment groups at the following time points: baseline (psilocybin first n=14, niacin first n=15), 1 day pre-dose 1 (psilocybin first n=14, niacin first n=15), 1 day post-dose 1 (psilocybin first n=14, niacin first n=15), 2 weeks post-dose 1 (psilocybin first n=14, niacin first n=14), 6 weeks post-dose 1 (psilocybin first n=14, niacin first n=14), 7 weeks post-dose 1 (psilocybin first n=12, niacin first n=14). Asterisks indicate significance level of between-group t-tests. Effect sizes, represented as Cohen's d, are shown above time points at which the treatment groups differ. Closed points represent significant within-group differences relative to scores at baseline.

Subjective drug effects/mystical experience was assessed at 7 hours after drug administration sessions and retrospectively at 26 weeks post-dose 2: the Mystical Experience Questionnaire (MEQ 30) (Barrett et al., 2015) is a self-report questionnaire that evaluates discrete mystical experiences induced by serotoninergic psychedelics and is sensitive to detecting psilocybin-induced mystical experiences (MacLean et al., 2012). In addition to an MEQ total score, the questionnaire generates four empirically derived factors: mystical; positive mood; transcendence of time and space; and ineffability. A retrospective version of the MEQ 30 (MEQ retrospective scale) was administered at 26 weeks post-dose 2. See Supplementary Methods section for more information on the MEQ 30 and for other measures of subjective drug effects/mystical experience measured 7 hours after drug administration sessions.

Persisting effects of psilocybin were assessed at 2 weeks post-dose 1 and 26 weeks post-dose 2: the Persisting Effects Questionnaire (PEQ), a self-report measure of changes in attitudes, moods, behaviors and spiritual experiences, sensitive to the longitudinal effects of psilocybin administration (Griffiths et al., 2006, 2008, 2011). All participants (including in both the psilocybin first and niacin first groups) were asked at 26 weeks after dose 2 to reflect on the meaningfulness, spiritual significance and changes in wellbeing relative to what they guessed was their psilocybin dosing experience (see Supplementary Methods secondary outcome measures).

See Supplementary Methods for other secondary outcome measures.

Statistical analysis

Whenever multiple time points were included in the analysis for continuous measures, repeated measures regressions, from the mixed effect repeated measurement (MMRM) model, were performed in SAS PROC MIXED using an AR(1) covariance structure and fixed effects of group and time. Comparison t-tests from the MMRM analyses are reported for the primary and the continuous secondary outcome measures (see below).

For the primary outcome measures (anxiety, depression) in the two dosing sequences, planned between-group comparisons were made at the following time points: prior to the crossover at baseline, 1 day pre-dose 1, 1 day post-dose 1, 2 weeks post-dose 1, 6 weeks post-dose 1, 7 weeks post-dose 1 (corresponding to 1 day pre-dose 2) (Figure 3) and after the crossover at 1 day post-dose 2, 6 weeks post-dose 2, and 26 weeks post-dose 2 (Figure 4). Between-group effect sizes were calculated using Cohen's d.

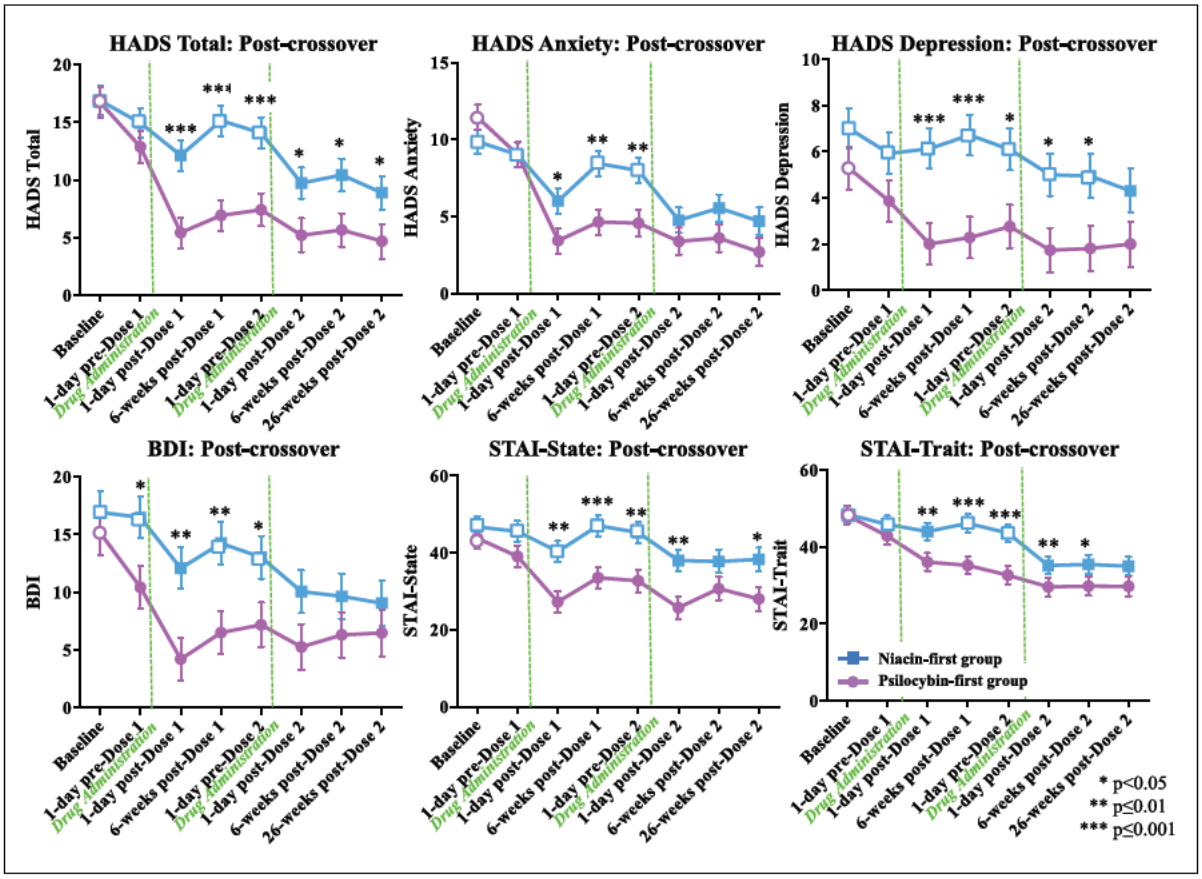


Figure 4. Primary outcome variables: cancer-related anxiety and depression (post-crossover).
Means (±SE) for primary outcome measures are shown in the two treatment groups at the following time points: baseline (psilocybin first *n*=14, niacin first *n*=15), 1-day pre dose-1 (psilocybin first *n*=14, niacin first *n*=15), 1 day post-dose 1 (psilocybin first *n*=14, niacin first *n*=15), 6 weeks post-dose 1 (psilocybin first *n*=14, niacin first *n*=14), 7 weeks post-dose 1 (1 day pre-dose 2) (psilocybin first *n*=12, niacin first *n*=14), 1 day post-dose 2, 6 weeks post-dose 2 (psilocybin first *n*=12, niacin first *n*=11), 26 weeks post-dose 2 (psilocybin first *n*=11, niacin first *n*=12). Asterisks indicate significance level of between-group *t*-tests. Closed points represent significant within-group differences relative to scores at baseline.

Planned within-group comparison *t*-tests were conducted for each of the dosing sequences comparing the baseline to each of the following time points: 1 day pre-dose 1, 1 day post-dose 1, 2 weeks post-dose 1, 6 weeks post-dose 1, 7 weeks post-dose 1 (1 day pre-dose 2), 1 day post-dose 2, 6 weeks post-dose 2, 26 weeks post-dose 2 (Figures 3 and 4). Within-group effect sizes for the dosing sequences were calculated at each time point, compared to baseline, using Cohen's d (Supplementary Table 1). To assess whether the magnitude of psilocybin-induced change in anxiety and depression differed across treatment groups, we compared change scores on the six primary outcome measures across each participant's active (psilocybin) treatment session (from 1 day prior to psilocybin treatment to 1 day after psilocybin treatment) with one-way analysis of variance (ANOVA).

For primary outcome measures (HAD D, BDI, HAD A, HAD T) that have empirical support in defining anti-depressant or anxiolytic response, clinically significant responses rates were defined as a 50% or greater reduction in the measure at a particular assessment point relative to baseline. Anti-depressant symptom remission (HAD D, BDI) was defined as 50% or greater reduction in depressive symptoms plus HADS D ⩽7 (Hung et al., 2012) or BDI ⩽12 (Reeves et al., 2012; Riedel et al., 2010), respectively. Planned chi-square analyses were performed to compare the percentage of participants, in the psilocybin first versus the niacin first groups, who met criteria for anxiolytic or anti-depressant response, or anti-depressant remission (BDI, HAD D) at the following time points: 1 day post-dose 1, 7 weeks post-dose 1, and 26 weeks post-dose 2 (Figure 5).

For cardiovascular measures assessed during the medication sessions, repeated measures regressions, from the mixed effect repeat measurement (MMRM) model, were conducted in SAS PROC MIXED using an AR(1) covariance structure and fixed effects of time, drug (psilocybin vs. niacin) and group (niacin first vs. psilocybin first) collapsed across treatment order at time points: baseline, 30, 60, 90, 120, 180, 240, 300, 360 post-dosing (Supplementary Figure 1).

For the secondary outcome measures (cancer-related existential distress, quality of life, spirituality, persisting effects of psilocybin), planned between-group comparisons were conducted generating the following comparisons: 1. niacin first group 2 weeks post-dose 1 versus psilocybin first group 2 weeks post-dose 1; 2. niacin first group 2 weeks post-dose 1 versus niacin first group 26 weeks post-dose 2; 3. niacin first group 2 weeks post-dose 1 versus psilocybin first group 26 weeks post-dose 2; 4. psilocybin first group 2 weeks post-dose 1 versus psilocybin first group 26 weeks post-dose 2 (Figure 6 (bottom), Supplementary Table 2).

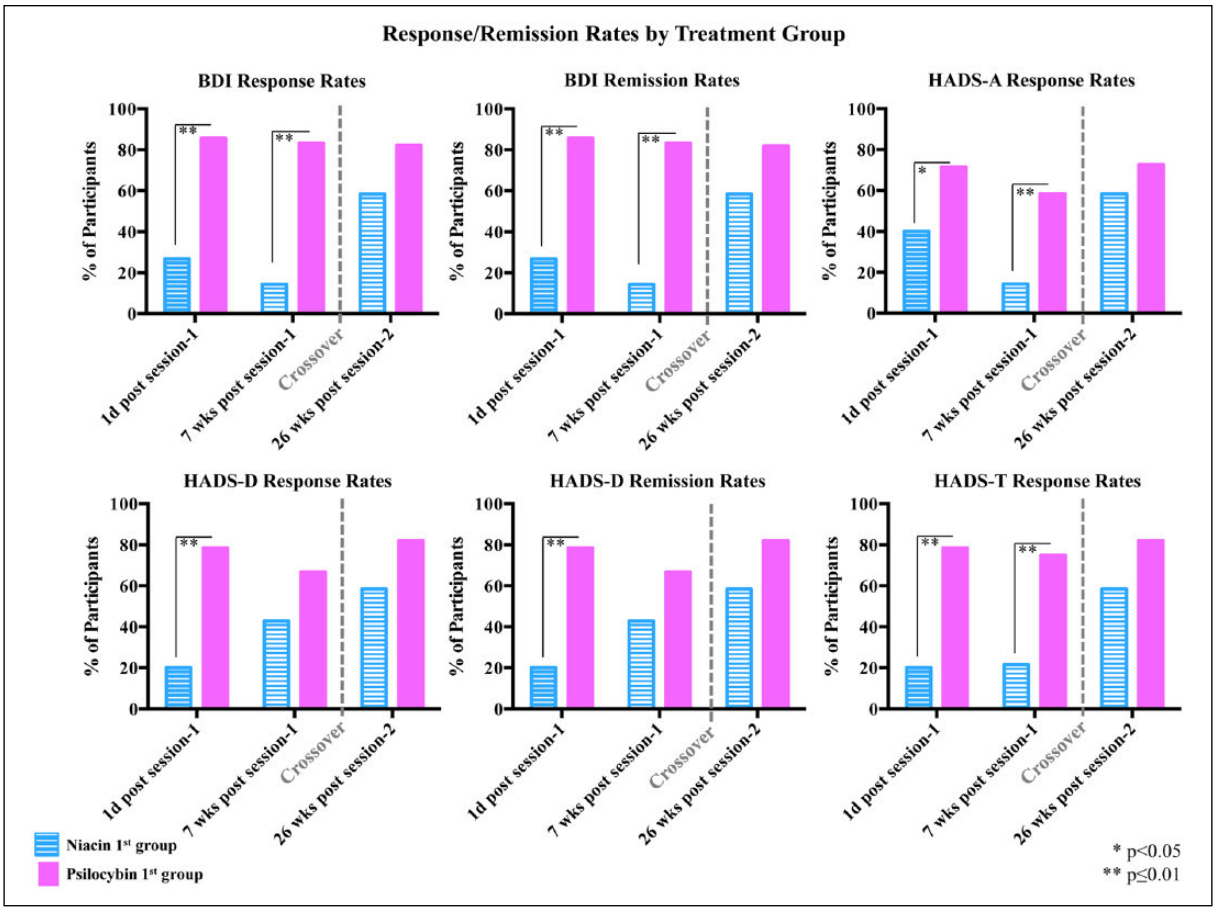


Figure 5. Percentage of participants with anti-depressant or anxiolytic response rates and anti-depressant symptom remission.
Percentages of participants in each treatment group who met criteria for anti-depressant or anxiolytic response or anti-depressant symptom remission (BDI, HAD D) at 1 day post-dose 1 (psilocybin first *n*=14, niacin first *n*=15), 7 weeks post-dose 1 (psilocybin first *n*=12, niacin first *n*=14) and at 26 weeks post-dose 2 (psilocybin first *n*=11, niacin first *n*=12). Asterisks indicate significance level of between-group comparisons at each time point.

Ratings of persisting effects attributed to the medication sessions were expressed as proportions for four items (see Supplemental Methods): positive behavioral change; meaningfulness, spiritual significance, and increases in personal wellbeing. Planned chi-square analyses were performed: niacin first group at 2 weeks post-dose 1 and psilocybin first at 2 weeks post-dose 1, niacin first at 2 weeks post-dose 1 and psilocybin first at 26 weeks post-dose 2. McNemar tests were used to compare these proportions between the psilocybin first group at 2 weeks post-dose 1 and the psilocybin first group at 26 weeks post-dose 2 and between the niacin first group at 2 weeks post-dose 1 and the niacin first group at 26 weeks post-dose 2 (Figure 6 (top)).

Subjective drug effects/mystical experiences were compared between groups using an independent sample *t*-test run in SAS at three time points: 7 hours post-medication administration in sessions 1 and 2; and at 26 weeks post-dose 2 (Figure 7 (top)). Anxiety and depression change scores for the primary outcome measures (ΔHADS T, ΔHADS A, ΔHADS D, ΔBDI, ΔSTAI S, ΔSTAI T) were calculated from baseline to 6 weeks post-dose 1 with either psilocybin or niacin. Spearman rank correlation coefficients were calculated between the change scores and participant ratings on the MEQ total at 7 hours post-dose 1 to assess the relationship between subjective mystical experience and change in clinical outcomes. Significant relationships were further examined using partial correlations to control for end of session participant-rated 'intensity' (item 98 from the HRS). In order to examine the mystical experience (using MEQ 30 scores) as a mediator of psilocybin versus niacin treatment on anxiety/depression outcomes, a bootstrap analysis was performed using the PROCESS macro (Hayes, 2013, Figure 7 (bottom)). The bootstrapping method is a non-parametric approach that does not assume a normal distribution of the mediated effect, is appropriate with small sample sizes, and was used to estimate 95% confidence intervals (CIs) for the mediation effect (Hayes, 2013). See Supplemental Methods.

See Supplementary Methods for additional statistical analysis.

Results

Demographics

As reported in Table 1, of the 29 participants who completed dose 1, the majority were Caucasian (90%) and women (62%). The average age was 56.3 (range 22–75) years. Approximately half of the participants reported some organized religious faith versus

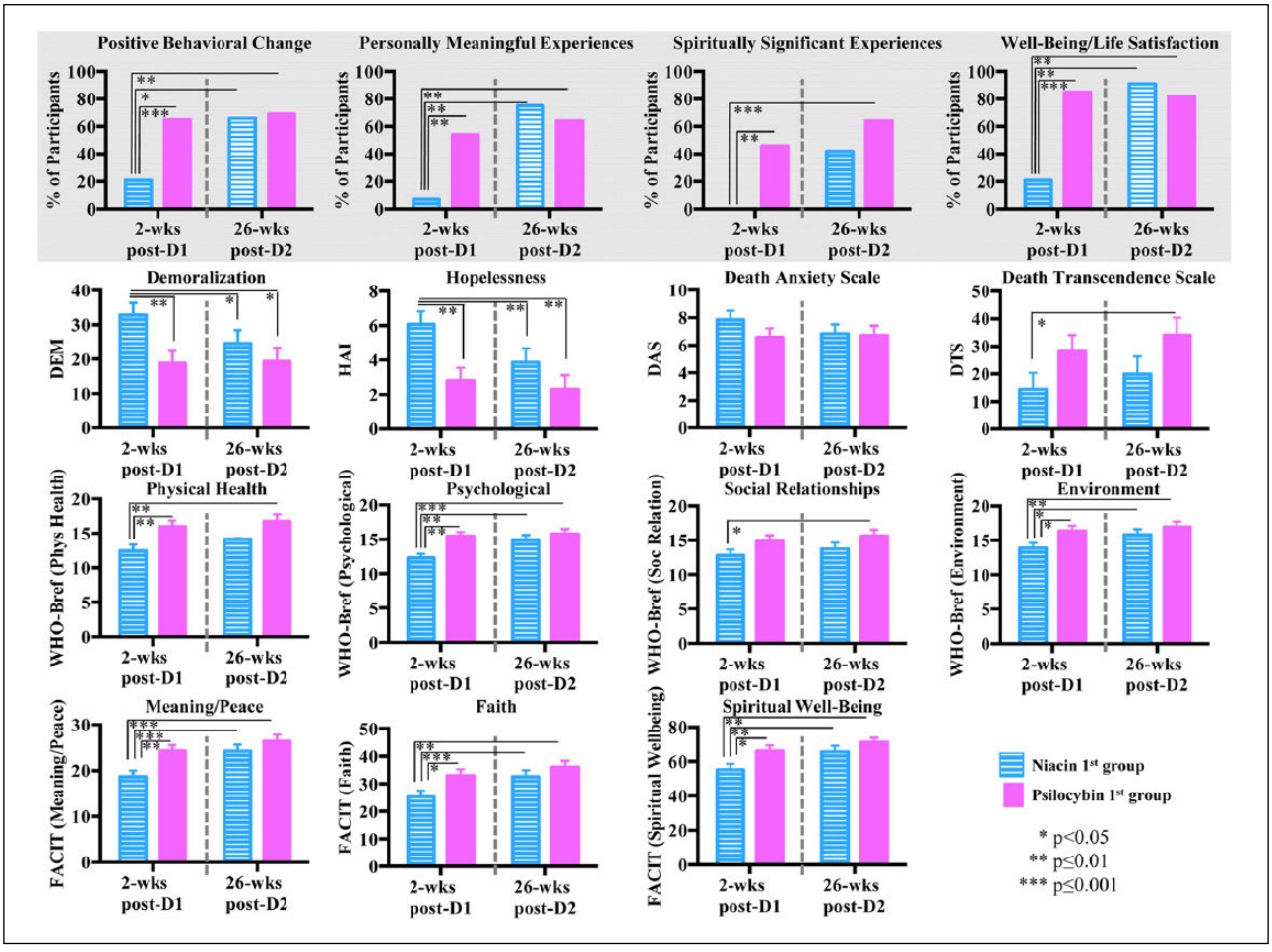


Figure 6. Secondary outcome measures: existential distress, quality of life, spirituality, persisting effects attributed to psilocybin administration. (Top) Percentage of participants that reported 'among the top 5' or 'the single most' personally meaningful and spiritually significant experiences, 'moderate', 'strong' or 'extreme' positive behavioral change, and 'increased moderately' or 'increased very much' wellbeing or life satisfaction on the Persisting Effects Questionnaire (PEQ). Asterisks indicate significance level of comparison to the niacin first group at 2 weeks post-dose 1. There were no significant differences between the psilocybin first group at 2 weeks post-dose 1 versus the psilocybin first group at 26 weeks post-dose 2. (Bottom) Secondary measures of cancer-related existential distress (DEM, HAI, DAS, DTS), quality of life (WHO-Bref) and spirituality (FACIT). Measures are shown at 2 weeks post-dose 1 (psilocybin first n=14, niacin first n=14) and at 26 weeks post-dose 2 (psilocybin first n=11, niacin first n=12); asterisks indicate significance level of comparison to the niacin first group at 2 weeks post-dose 1. There were no significant differences between the psilocybin first group at 2 weeks post-dose 1 versus the psilocybin first group at 26 weeks post-dose 2.

atheist/agnostic (52% vs. 48%) and slightly less than half reported no prior history of hallucinogen use (45%). Ninety per cent of participants met DSM-IV criteria for cancer-related adjustment disorder with anxious ± depressed features. The two dose-sequence groups did not significantly differ on demographic or clinical characteristic measures. No dichotomous factors (i.e. gender, prior hallucinogen use vs. none, spiritual faith/religion vs. none, early vs. late cancer stage) significantly interacted with the primary outcome measures in between-group comparisons.

Safety assessments

Adverse events. There were no serious AEs, either medical or psychiatric, in the trial that were attributed to either psilocybin or niacin. Regarding psychiatric AEs, no pharmacological interventions (e.g. benzodiazepines, anti-psychotics) were needed during dosing sessions, no participants abused or became addicted to psilocybin, there were no cases of prolonged psychosis or hallucinogen persisting perceptual disorder (HPPD), and no participants required psychiatric hospitalization. In terms of AEs attributable to psilocybin, the most common medical AEs were non-clinically significant elevations in BP and HR (76%), headaches/migraines (28%), and nausea (14%); the most common psychiatric AEs were transient anxiety (17%) and transient psychotic-like symptoms (7%: one case of transient paranoid ideation and one case of transient thought disorder). The medical AEs (non-clinically significant elevations in BP and HR, headaches, nausea), and psychiatric AEs (transient anxiety, transient near-psychotic symptoms) attributable to psilocybin are all known AEs of psilocybin, were transient, tolerable, and consistent with prior trials of psilocybin administration in normal volunteers (Griffiths et al., 2006, 2008, 2011), and patients with terminal cancer (Grob et al., 2011).

Cardiovascular effects during dosing sessions. Compared to the control, psilocybin produced statistically significant

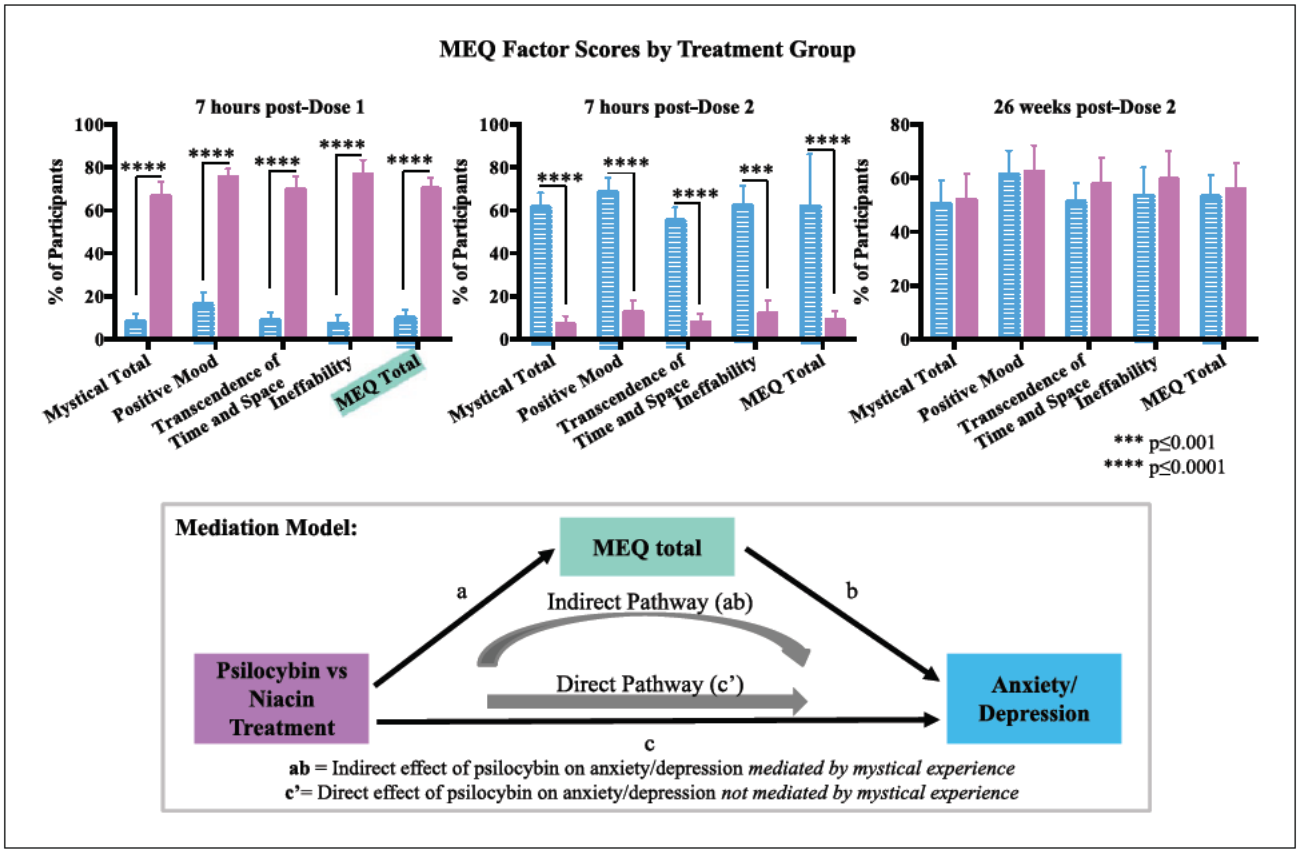


Figure 7. Subjective effects of psilocybin and relationship of mystical experience to clinical outcomes.
(Top) Subjective effects as measured by the Mystical Experience Questionnaire (MEQ 30) in each treatment group at 7 hours post-session 1 (psilocybin first *n*=14, niacin first *n*=15), 7 hours post-session 2 (psilocybin first *n*=12, niacin first *n*=14), and 26 weeks post-dose 2 (psilocybin first *n*=11, niacin first *n*=12). Asterisks indicate significance level of between-group differences. (Bottom) Mediation model in which total scores on the MEQ transmit a portion of the effects of psilocybin versus niacin treatment on change in anxiety and depression is shown.

differences in the following cardiovascular measures and time points: systolic BP: 60, 90, 120, 180, 240, 300 minutes; diastolic BP 60, 90, 120, 180 minutes; pulse: 90, 120 minutes (see Supplementary Figure 1). Cardiovascular effects with psilocybin generally peaked at 180 minutes post-dosing and decreased towards pre-drug levels over the remainder of the session. Regarding the psilocybin first group, peak mean systolic and diastolic BPs were 142/83 (both recorded at 180 minutes post-dosing), while peak mean HR for this group was 71 at 300 minutes post-dosing (see Supplementary Figure 1). There were no serious adverse cardiac events, consistent with psilocybin's absence of cardiac toxicity when administered in controlled laboratory settings (Studerus et al., 2011). The medical safety, time course, and magnitude of effects on these cardiovascular measures were consistent with those observed in previous studies of psilocybin in healthy volunteers (Griffiths et al., 2006, 2011) and patients with advanced cancer (Grob et al., 2011).

Primary outcomes

For each of the six primary outcome measures (HADS T, HADS A, HADS D, BDI, STAI S, STAI T), there were significant differences between the experimental and control groups (prior to the crossover at 7 weeks post-dose 1) with the psilocybin group (compared to the active control) demonstrating immediate, substantial, and sustained (up to 7 weeks post-dosing) clinical benefits in terms of reduction of anxiety and depression symptoms (Figure 3). The magnitude of differences between the psilocybin and control groups (Cohen's d effect sizes) was large across the primary outcome measures, assessed at 1 day/2 weeks/6 weeks/7 weeks post-dose 1 (Figure 3).

Treatment groups did not differ in magnitude of change (e.g. 1 day before compared to 1 day after) across their respective psilocybin treatment sessions for any of the primary outcome measures (BDI: $F_{(1,26)}$=1.88, P=0.18; HADS A: $F_{(1,26)}$=2.59, P=0.12; HADS D: $F_{(1,26)}$=0.90, P=0.35; HADS T: $F_{(1,26)}$=2.63, P=0.12; STAI S: $F_{(1,26)}$=1.10, P=0.30; STAI T: $F_{(1,26)}$=0.58, P=0.45).

For all primary outcome measures, the psilocybin first group demonstrated significant within-group reductions (compared to baseline at each post-baseline assessment point) in anxiety and depression immediately after receiving psilocybin (Figures 3 and 4). These reductions remained significant at each time point, including the final point at 26 weeks post-dose 2 (approximately 8 months), post-psilocybin dosing. Prior to the crossover, the niacin first group demonstrated either no significant within-group reductions or a transient reduction that became non-significant prior to dose 2. For the majority (five/six) of the measures, the niacin first group demonstrated significant within-group

reductions in anxiety and depression immediately after receiving the psilocybin dose (dosing session 2), and these statistically significant improvements persisted until the end of the study (approximately 6.5 months post-psilocybin dosing, 26 weeks post-dose 2, for this group).

Psilocybin produced immediate and enduring anxiolytic and anti-depressant response rates, as well as significant anti-depressant remission rates (measured by the HADS D and BDI) (Figure 5). For example, 7 weeks after dose 1, 83% of participants in the psilocybin first group (vs. 14% in the niacin first group) met criteria for anti-depressant response (with the BDI) and 58% (in the psilocybin first group) for anxiolytic response using the HAD A, compared to 14% in the niacin first group. At the 6.5-month follow-up (after both groups received psilocybin), anti-depressant or anxiolytic response rates were approximately 60–80% (Figure 5).

Secondary outcomes

Figure 6 (bottom) shows the comparisons between dose-sequence groups on the following secondary outcome measures: cancer-related existential distress (demoralization, hopelessness, attitudes and affect associated with disease progression and death), quality of life, and spirituality. In the short-term (2 weeks post-dose 1), psilocybin (compared to control) produced decreases in cancer-related demoralization and hopelessness, while improving spiritual wellbeing and quality of life (physical, psychological, environmental domains). These effects were sustained at the final 6.5 month follow-up. Regarding anxiety and attitudes towards death, the data were mixed. In the short-term (2 weeks post-dose 1), psilocybin was not significantly associated with decreased death anxiety or increased death transcendence. However, at the 26-week post-dose 2 final follow-up assessment, while death anxiety (as measured by the DAS) continued to demonstrate no significant reductions, there was a significant improvement in attitudes and adaptations towards death (as measured by the DTS) in the psilocybin first group compared to the niacin first group (assessed at 2 weeks post-dose 1).

Supplementary Table 2 shows participant ratings of persisting effects attributed to the session experiences. As shown, prior to the crossover, psilocybin produced significantly greater ratings (compared to the niacin first group assessed at 2 weeks post-dose 1) of positive persisting effects on: attitudes about life and self, mood changes, social effects (e.g. increased altruism), behavior, and spirituality. After the crossover, these effects were sustained at the final 6.5-month follow-up. When all participants were asked (26 weeks post-session 2) to reflect on what they thought was their psilocybin session, 52% and 70% rated the psilocybin experience as the singular or top 5 most spiritually significant, or the singular or top 5 most personally meaningful experience of their entire lives, respectively; while 87% reported increased life satisfaction or wellbeing attributed to the experience (Figure 6 (top)).

Mystical experience subjective effects and relationship of mystical experience to clinical outcomes

Compared to the control, psilocybin produced mystical-type experiences, consistent with prior trials of psilocybin administration in normal volunteers (Griffiths et al., 2006, 2008, 2011) and patients with terminal cancer (Grob et al., 2011) (Figure 7 (top)). Total mystical experience scores (MEQ 30) at the end of dose 1 (e.g. 7 hours post-drug administration) correlated with change scores (baseline to 6 weeks after dose 1) on four out of six primary outcome measures: HADS T (Spearman r=0.39; P=0.04); HADS A (Spearman r=0.36; P=0.07); HADS D (Spearman r=0.30; P=0.11); BDI (r=0.49; P=0.01); STAI S (r=0.42; P=0.03); STAI T (r=0.39; P=0.04).

Partial correlations to control for participant-rated intensity of drug effect (item 98 from the HRS) continued to demonstrate significant effects of total mystical experience scores (MEQ total) on the change scores (baseline to 6 weeks after dose 1) of the primary outcome measures in five of six measures assessed: HADS T (Spearman r=0.49; P=0.009); HADS A (Spearman r=0.46; P=0.01); HADS D (Spearman r=0.35; P=0.07); BDI (r=0.48; P=0.01); STAI S (r=0.42; P=0.03); STAI T (r=0.40; P=0.04).

MEQ total scores mediated (indirect effects) a significant portion of the effect of psilocybin versus niacin treatment on four out of six primary outcome measures with point estimates (ab) and bias corrected 95% CIs as follows: (HADS T (ab=0.46, SE=0.24, 95% CI 0.01–0.97), HADS D (ab=0.43, SE=0.32, 95% CI 0.01–1.23), BDI (ab=0.79, SE=0.26, 95% CI 0.23–1.29), and STAI S (ab=0.65, SE=0.25, 95% CI 0.13–1.16)] (Figure 7 (bottom)). Thus, the amount by which ΔHADS T, ΔHADS D, ΔBDI, and ΔSTAI S can be expected to increase through MEQ total as a result of psilocybin versus niacin treatment is 0.46, 0.43, 0.79 and 0.65, respectively.

For other analyses of secondary outcome measures, see Supplementary Results.

Discussion

Primary outcomes

Single moderate-dose psilocybin, in conjunction with psychotherapy, produced rapid, robust, and sustained clinical benefits in terms of reduction of anxiety and depression in patients with life-threatening cancer. This pharmacological finding is novel in psychiatry in terms of a single dose of a medication leading to immediate anti-depressant and anxiolytic effects with enduring (e.g. weeks to months) clinical benefits. Even though it is not possible to attribute causality of the experimental drug (in terms of sustained clinical benefit) after the crossover, the post-crossover data analyses of the two dosing sequences suggest that the clinical benefits, in terms of reduction of cancer-related anxiety and depression, of single-dose psilocybin (in conjunction with psychotherapy) may be sustained for longer than 7 weeks post-dosing, and that they may endure for as long as 8 months post-psilocybin dosing. The acute and sustained anti-depressant effects of psilocybin in this trial are consistent with a recently published open-label study of oral psilocybin treatment in patients with treatment-resistant depression (TRD) in which psilocybin (25 mg) was associated with 1 week and 3 months post-psilocybin anti-depressant effects (Carhart-Harris et al., 2016).

The within-group analyses for the primary outcome measures demonstrate that immediately after receiving psilocybin there is a marked reduction in anxiety and depression scores for both the psilocybin first and niacin first groups. Also, the magnitude of psilocybin-induced change across each participant's active

psilocybin treatment session did not differ across treatment group for any of the primary outcome measures. Together, this suggests that the pharmacological/psilocybin intervention produced rapid anti-depressant and anxiolytic clinical benefits. Both groups demonstrated significant clinical improvements in anxiety/depression from baseline relative to the final assessment. It is unclear from the data whether the sustained benefits in clinical outcomes were due to psilocybin alone or some interactive effect of psilocybin plus the targeted psychotherapy. Future research would be necessary to separate out the various therapeutic contributions of psilocybin versus psychotherapy.

Psilocybin was associated with substantial anti-depressant response rates (as high as approximately 80% at 6.5 months follow-up). There have been several meta-analyses of placebo controlled trials exploring the efficacy of anti-depressants in the treatment of cancer-related depression and they have generally failed to show a clear effect of anti-depressant treatment over placebo (Iovieno et al., 2011; Laoutidis and Mathiak, 2013; Ostuzzi et al., 2015). In a meta-analyses of anti-depressants for major depressive disorder in patients with comorbid medical disorders (including cancer), anti-depressants were more effective than placebo in some medical conditions (e.g. HIV/AIDS, post-stroke) but not in cancer patients, where the anti-depressants performed about as well as the approximately 40% placebo response rate (Iovieno et al., 2011).

Secondary outcomes

Psilocybin decreased cancer-related demoralization (e.g. loss of meaning/hope/purpose, desire for hastened death) and hopelessness, while improving spiritual wellbeing, general life satisfaction, and quality of life. While a minority of patients with advanced or terminal cancer experience clinically relevant existential/spiritual distress, when it occurs its effects are highly consequential (e.g. decreased quality of life, increased depressive and anxiety symptoms, increased desire for hastened death, increased suicidal ideation and behaviors) (Puchalski, 2012) and improving spiritual wellbeing (e.g. through a pharmacological-psychosocial intervention) could serve as a buffer against these negative clinical outcomes.

Although affect/anxiety towards death did not improve in the short-term or longer-term follow-up period, psilocybin was associated with improved attitudes and adaptations to death at the 6.5-month follow-up. More research into this important therapeutic area is warranted.

Psilocybin experiences were reported as highly meaningful and spiritual, and associated with positive cognitive, affective, spiritual, and behavioral effects lasting weeks to months. This finding is consistent with prior research administering psilocybin to normal volunteers (Doblin, 1991; Griffiths et al., 2006, 2008, 2011; Pahnke, 1963).

Safety/adverse events

There were no serious AEs, either medical or psychiatric, in the trial that were attributed to psilocybin. Since the early 1990s, approximately 2000 doses of psilocybin (ranging from low to high doses) have been safely administered to humans in the United States and Europe, in carefully controlled scientific settings, with no reports of any medical or psychiatric serious AEs, including no reported cases of prolonged psychosis or HPPD (Studerus et al., 2011). This finding is consistent with a US population (2001–2004 data from the National Survey on Drug Use and Health) based study that found no associations between lifetime use of any of the serotoninergic psychedelics (including psilocybin) and increased rates of mental illness (Krebs and Johansen, 2013). It is important to monitor closely for the emergence of transient difficult psychological states (e.g. anxiety, paranoia) in these trials and to manage them. Difficult experiences are not necessarily pathological and can be understood as part of the therapeutic process (e.g. working through cancer-related psychological or existential distress through challenging encounters or emotionally charged confrontations with cancer-related fearful imagery or symbolism) (Carbonaro et al., 2016).

Limitations/generalizability

This trial was limited by a relatively small sample size, a non-nationally representative cancer patient population (e.g. 62% women, 90% Caucasian), which decreases generalizability, a crossover design that limited the interpretation of clinical benefits after the crossover, and the use of a control with limited blinding.

Potential anxiolytic and anti-depressant mechanisms of psilocybin

Neurobiological mechanisms. There is evidence from animal research that serotoninergic psychedelics exert anxiolytic-like effects (Nichols, 2015). Several trials using animal models of anxiety demonstrated acute anxiolytic effects of the serotoninergic psychedelic 2,5-Dimethoxy-4-iodoamphetamine (DOI), a non-selective 5-HT2a/2c agonist (Nic Dhonnchadha et al., 2003; Ripoll et al., 2005, 2006). In two rodent studies, one with 5HT2A knockout mice (Weisstaub et al., 2006) and the other in rats with anti-sense-mediated 5HT2A downregulation (Cohen, 2005), the rodents displayed decreased anxiety-like behavior and in the trial with the 5HT2A knockout mice (Weisstaub et al., 2006), restoration of 5HT2A receptors in the pre-frontal cortex (PFC) re-established anxiety-like behaviors. Furthermore, in humans, fronto-limbic 5HT2A density has been correlated with anxiety symptoms (Frokjaer et al., 2008). Together, these data suggest that 5HT2A downregulation may explain some of the rapid and sustained anxiolytic effects of psilocybin (Vollenweider and Kometer, 2010).

There is growing evidence that the serotoninergic psychedelics produce rapid and sustained anti-depressant effects (Nichols, 2015). In two recently published open-label trials, one using a single dose of ayahuasca (Osorio et al., 2015) and the other using two doses of oral psilocybin (Carhart-Harris et al., 2016), acute and enduring anti-depressant effects were reported. In addition to these two open-label trials, there are several lines of evidence supporting using 5HT2A agonists to treat depression. In considering changes at the 5HT2A receptor as a potential mechanism of action: cortical 5HT2A receptor expression is increased in postmortem samples of patients with depression who display suicidality (Mendelson, 2000; Pandey et al., 2002; Shelton et al., 2009); depressed patients with elevated pessimism

display increased PFC 5HT2A receptor binding compared to control participants (Bhagwagar et al., 2006; Meyer, 2012; Meyer et al., 2003); and sustained treatment with various anti-depressants (e.g. selective serotonin reuptake inhibitors, tricyclic antidepressants) have been associated with a reduction of 5HT2A receptor density (Gomez-Gil et al., 2004; Yamauchi et al., 2006).

The glutamate system may explain some of the anti-depressant effects of psilocybin. In rodents, serotoninergic psychedelics enhance cortical glutamatergic transmission, especially in the medial PFC, and increase activation of cortical α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Aghajanian and Marek, 1997). In a trial in which rats received DOI, there was a significant increase in expression of brain-derived neurotrophic factor (BDNF) mRNA in neocortical areas (Vaidya et al., 1997). Increased AMPA activation and BDNF expression as biomarkers of anti-depressant effects are supported by: cortical AMPA activation is known to stimulate the expression of cortical BDNF (associated with neuronal growth, differentiation and synaptogenesis) (Hsu et al., 2015); decreased cortical BDNF is associated with major depression in humans (Duman, 2004); and cortical BDNF normalizes with anti-depressant treatment (Sen et al., 2008; Shimizu et al., 2003). Similarly, ketamine (the only other known acute and short-term sustained anti-depressant) is theorized to exert its anti-depressant effects via cortical AMPA activation (Zanos et al., 2016) and BDNF expression (Lepack et al., 2014). However, the anti-depressant effects of single-dose ketamine in patients with TRD typically last no more than several days up to 1–2 weeks, not several weeks to months (DeWilde et al., 2015).

Neuroimaging research with psilocybin is beginning to suggest potential anti-depressant mechanisms of action at the level of brain structure activity and network connectivity. Task-free functional magnetic resonance imaging research in normal volunteers under the influence of psilocybin has demonstrated decreased activity in the medial PFC and decreased connectivity within the default mode network (DMN) (Carhart-Harris et al., 2012, 2014). The former is significant because depressive symptoms have been associated with increased activity in the medial PFC (Drevets et al., 2008; Farb et al., 2011) and normalization of medial PFC activity has been demonstrated with anti-depressant treatment (Deakin et al., 2008; Holtzheimer and Mayberg, 2011; Kennedy et al., 2007); and the latter because patients with major depression (compared to controls) have demonstrated increased DMN connectivity (Berman et al., 2011, Grecius et al., 2007).

Psycho-spiritual mechanisms. Moderate-dose psilocybin occasioned mystical-type experiences in the cohort of cancer patients studied, and the intensity of the subjective mystical experience significantly mediated (e.g. suggestive of causality) clinical benefit (e.g. reduction in anxiety and depression symptoms) in the medium term (e.g. 6 weeks post-dose 1). This result matches with descriptive historical data from open-label LSD-assisted psychotherapy trials for psycho-spiritual distress associated with terminal cancer, in which the mystical experience was reported as being an integral part of the therapeutic effect (Grof and Halifax, 1977). It is further corroborated by recent open-label trials using psilocybin-assisted psychotherapy to treat tobacco addiction (Garcia-Romeu et al., 2014; Johnson et al., 2014) and alcoholism (Bogenschutz et al., 2015) showing significant correlations between the mystical experience and improved clinical outcomes.

This finding suggests a potential psycho-spiritual mechanism of action: the mystical state of consciousness. The mystical experience is likely to be one of several mediators that transmit the effect of psilocybin to changes in anxiety and/or depression. Further enquiry into how particular dimensions of the mystical experience relate to reductions in anxiety and/or depression in this population and others, and what factors best predict or promote mystical experiences, is warranted.

Conclusions

In conclusion, single moderate-dose psilocybin (in conjunction with psychotherapy) was safely administered to a cohort of patients with cancer-related psychological distress (e.g. anxiety, depression). It produced rapid and sustained anxiolytic and anti-depressant effects (for at least 7 weeks but potentially as long as 8 months), decreased cancer-related existential distress, increased spiritual wellbeing and quality of life, and was associated with improved attitudes towards death. The psilocybin-induced mystical experience mediated the anxiolytic and anti-depressant effects of psilocybin. Psilocybin, administered in conjunction with appropriate psychotherapy, could become a novel pharmacological-psychosocial treatment modality for cancer-related psychological and existential distress. Further empirical research is needed definitively to establish its safety and efficacy.

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Author comment on supplementary materials

The authors affirm that the research materials relating to this paper can be accessed.

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Human hallucinogen research: guidelines for safety

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Abstract

There has recently been a renewal of human research with classical hallucinogens (psychedelics). This paper first briefly discusses the unique history of human hallucinogen research, and then reviews the risks of hallucinogen administration and safeguards for minimizing these risks. Although hallucinogens are relatively safe physiologically and are not considered drugs of dependence, their administration involves unique psychological risks. The most likely risk is overwhelming distress during drug action ('bad trip'), which could lead to potentially dangerous behaviour such as leaving the study site. Less common are prolonged psychoses triggered by hallucinogens. Safeguards against these risks include the exclusion of volunteers with personal or family history of psychotic disorders or other severe psychiatric disorders, establishing trust and rapport between session monitors and volunteer before the session, careful volunteer preparation, a safe physical session environment and interpersonal support from at least two study monitors during the session. Investigators should probe for the relatively rare hallucinogen persisting perception disorder in follow up contact. Persisting adverse reactions are rare when research is conducted along these guidelines. Incautious research may jeopardize participant safety and future research. However, carefully conducted research may inform the treatment of psychiatric disorders, and may lead to advances in basic science.

Key words

5 HT_{2A} agonists; adverse reactions; DMT; entheogens; hallucinogens; human research; LSD; mescaline; psilocybin; psychedelics; safety guidelines

Introduction

After several decades of dormancy, research involving the administration of classical hallucinogens to humans has been recently renewed (Sessa, 2005; Frecska and Luna, 2006; Har vard Mental Health Letter, 2006; Lancet, 2006; Morris, 2006; Winkelman and Roberts, 2007). Although nonhuman animal research during the intervening decades has substantially advanced our understanding of underlying neuropharmacolog ical mechanisms of the hallucinogens, the fact that human research with this historically important and widely used class of compounds remained inactive is remarkable (Nichols, 2004). Renewed human administration research began with the work of Rick Strassman, who initiated research on the effects of N,N dimethyltryptamine (DMT) at the University of New Mexico in the early 1990s (Strassman, 1991, 1996, 2001; Strassman and Qualls, 1994; Strassman, *et al.*, 1994, 1996). Sub sequently, investigators both in the USA and in Europe have developed human research programmes with hallucinogens. This new research has included basic science studies that have administered hallucinogens as tools for investigating cognitive neuroscience and perception (Gouzoulis Mayfrank, *et al.*, 1998a; Gouzoulis Mayfrank, *et al.*, 2002; Umbricht, *et al.*, 2003; Carter, *et al.*, 2004; Carter, *et al.*, 2005a,b), time perception (Wittmann, *et al.*, 2007), hallucinogen pharmacokinetics and metabolism (Hasler, *et al.*, 1997, 2002), model psychosis (Vollenweider, *et al.*, 1997, 1998, 1999, 2007; Gouzoulis Mayfrank, *et al.*, 1998a; Vollenweider and Geyer, 2001; Gouzoulis Mayfrank, *et al.*, 2005, 2006), and, recently in our laboratory, hallucinogens' reported facilitation of experiences having enduring personal meaning and spiritual significance (Griffiths, *et al.*, 2006). Recent clinical studies have administered hallucinogens to evaluate their safety and efficacy in the treatment of psychiatric disorders: specifically, anxiety related to advanced stage cancer (Grob, 2005) and obsessive compulsive disorder (Moreno, *et al.*, 2006). In addition, several studies have examined the effects of

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ayahuasca (also known as *hoasca* or *yagé*; an admixture containing DMT) in human volunteers outside of the USA (Grob, *et al*., 1996; Riba, *et al*., 2001). Because the United States Supreme Court has recently ruled in favour of the União do Vegetal (UDV; a syncretic Brazilian church that uses *ayahuasca* in the context of religious ceremonies) in their claim that the UDV's use of *ayahuasca* is protected under the Religious Freedom Restoration Act (Gonzales v. O Centro Espirita Bene ficiente União do Vegetal, 2006), *ayahuasca* use within this church setting may receive increased scientific investigation within the USA.

We use the word 'hallucinogen' herein to refer to the classical hallucinogens, sometimes called 'psychedelics', 'psychotomimetics' or 'entheogens' (Grinspoon and Bakalar, 1979; Ruck, *et al*., 1979; Ott, 1996; Metzner, 2004). Admittedly, the term 'hallucinogen' is not ideal for these substances, because perceptual changes are only one domain of their effects, and the typical perceptual changes engendered by hallucinogens at typical doses rarely include frank hallucinations (Grinspoon and Bakalar, 1979; Nichols, 2004; O'Brien, 2006). However, we use this term because it is the most widely used in the scientific litera ture. Although the term 'psychedelic' is widely used, it has the disadvantage of carrying considerable cultural connotation (i.e. its use as a descriptor of a style of music or art associated with Western counter culture of the 1960s). The terms 'psychotomi metic' (emphasizing model psychosis) and 'entheogen' (empha sizing mystical type experiences, i.e. phenomenologically indistin guishable from classically described mystical experiences) highlight only a single aspect (which may not occur reliably) of the much broader range of hallucinogen effects.

Hallucinogens can be divided structurally into two classes of alkaloids: the tryptamines, including psilocybin (prodrug con stituent of *Psilocybe* and several other mushroom genera), the semi synthetic d lysergic acid diethylamide (LSD), and DMT; and the phenethylamines, including mescaline (principle active constituent of peyote) and certain synthetic compounds (Grinspoon and Bakalar, 1979; Shulgin and Shulgin, 1991, 1997; Metzner, 2004, Nichols, 2004). The effects of these substances are primarily mediated by agonist action at 5 HT_{2A} receptors (Glennon, *et al*., 1984; Nichols, 2004; González Maeso, *et al*., 2007) and produce a generally similar profile of subjective effects (Hidalgo, 1960; Hollister and Hartman, 1962; Wolbach, *et al*., 1962a,b; Shulgin and Shulgin, 1991, 1997). Other classes of substances have sometimes been identified as 'hallucinogens', including 3,4 methylenedioxymethamphetamine or MDMA [perhaps more appropriately labelled an entactogen (Nichols, *et al*., 1986) or empathogen (Metzner, 1985)]; dissocia tive anaesthetics such as ketamine, phencyclidine and dextro methorphan; and anticholinergic agents such as scopolamine and atropine (Nichols, 2004). However, this paper uses the term 'hallucinogen' to refer specifically to classical hallucinogens.

The purpose of this paper is to provide guidance in the safe administration of high doses of hallucinogens (e.g. ≥25 mg psilocybin or 200 μg LSD). Some aspects of these recommenda tions may also apply to studies employing lower doses, although, as with other drug classes, the likelihood of potential adverse effects will be related to dose. Similarly, some aspects of these recommendations may also apply to studies administering the other drug classes mentioned in the preceding paragraph: entactogens, dissociative anaesthetics and anticholinergic agents. However, the clinical effects and mechanisms of action of these agents are sufficiently different from the classical hallucinogens that safety recommendations concerning their administration are beyond the scope of this manuscript.

First, so that the historical context in which current human hallucinogen studies are conducted will be clear, we will briefly discuss the history of sacramental hallucinogen use by indigenous cultures, and the history of human hallucinogen research before it became dormant in the 1970s. The decades long virtual dor mancy of human hallucinogen research stands as a unique case in the history of modern clinical pharmacology. It is important for researchers going forward to understand the role that safety factors, as well as sociological and political factors, played in the history and cessation of human hallucinogen research. Moreover, because of the historical legacy of sensationalism surrounding hallucinogens, researchers should appreciate the precarious posi tion of current human hallucinogen research, and recognize that very high safety standards will help to ensure that human research continues into the decades to come. Next, we will provide a detailed description of the unique risks of hallucinogen adminis tration. We will then present the proposed guidelines for conduct ing high dose hallucinogen research in each of several domains, including volunteer selection, study personnel, physical environ ment, preparation of volunteers, conduct of sessions, and post session procedures.

Relevant history

Hallucinogen use by indigenous cultures

Hallucinogens have been used by indigenous cultures for millennia (Schultes, 1969; Lowy, 1971; Schultes, *et al*., 2001). These cultures have restricted hallucinogen use to sacramental and healing contexts, with these two often being inseparably intertwined. Remarkably, apparently without exception, such cultures view hallucinogenic plants and fungi as being of divine origin (Schultes, *et al*., 2001). Given this orientation, it is not surprising that their ingestion is often tightly restricted, with use controlled by ceremonial guidelines, including taboos against improper use (Schultes, *et al*., 2001; Weil, 2004). Indigenous cultures restrict use of hallucinogens to highly ritualized, sacred ceremonies such as those designed to serve as rites of passage, or to set the occasion for divination and spiritual or physical healing. Even in cases in which certain use extends beyond the shaman and may be more recreational in nature (e.g. use of the DMT containing *epená* by the Waiká cultures of Brazil and Venezuela), the hallucinogen is prepared and taken in a highly ritualized context (Grinspoon and Bakalar, 1979; Schultes, *et al*. 2001; Weil, 2004). Modern, urban syncretic religions, such as the UDV, which have developed in South America and have been influenced by indigenous use of *ayahuasca*, also incorporate a high degree of structure and

guidance into their *ayahuasca* use, which may minimize adverse reactions (Gonzales v. O Centro Espirita Beneficiente União do Vegetal, 2006).

However, indigenous cultures should not be regarded as absolute role models in the clinical use of hallucinogens for at least two reasons. First, some of these cultures also engaged in practices considered unethical in our culture. For example, the Aztecs, who used psilocybin mushrooms and morning glory seeds (containing LSD related agents), practiced human sacrifice, and even incorporated hallucinogen use into sacrificial rituals (Ott, 1996). As another example, the Jivaro in Ecuador who use *ayahuasca* practice sacramental headhunting, and *ayahuasca* may be used by the shaman in that society for malevolent intent (i.e. bewitching) as well as for healing (Harner, 1962, 1968; Grof, 1977). Second, risk/benefit tradeoffs that may be acceptable in various religious contexts may fall short of what is expected in the domain of contemporary scientific research with human participants.

Nonetheless, some important themes have emerged in the use of hallucinogens by indigenous cultures that may have bearing on the appropriate use of hallucinogens in clinical research. Indeed, some of the safeguards developed for clinical hallucinogen research and expressed in the guidelines presented herein are similar to important aspects of hallucinogen use by indigenous cultures. These common themes are structured use (expressed as ritual in indigenous use), restrictions on use including the need for guidance and appreciation of hallucinogens' powerful psychological effects (expressed as reverence in indigenous use). We believe that these commonalities are more than coincidence. The unique pharmacology of classical hallucinogens may have shaped convergent practices across independent cultures. Likewise, the guidelines expressed herein for human clinical research with hallucinogens may also be viewed as having been developed in reaction to these same aspects of hallucinogen pharmacology. As an example, some of the unique effects and safety concerns for hallucinogens may be related to their ability to set the occasion for deeply meaningful, even spiritual experiences (Richards, 2003, 2005). Novak (1997) hypothesized that Western intellectuals in the mid 1950s such as Aldous Huxley and Gerald Heard merely redefined the subjective effects resulting from hallucinogen administration as a spiritual experience, thereby popularizing such an association in western culture. However, the observation that indigenous cultures that ingest classical hallucinogens almost invariably do so under sacramental contexts (Schultes, *et al.*, 2001), along with the findings from double blind clinical studies demonstrating that under supportive conditions, hallucinogens occasion mystical type experiences with high frequency (Pahnke, 1963; Griffiths, *et al.*, 2006) suggests that the association of hallucinogens with spiritual experience relates to the pharmacology of these agents rather than being based entirely on cultural suggestion.

Early clinical research

In the 1950s and 1960s, thousands of research participants were administered hallucinogens in the context of basic clinical research or therapeutic clinical research, resulting in hundreds of publications (Grinspoon and Bakalar, 1979; Grob, *et al.*, 1998; Strassman, 2001; Nichols, 2004). During this time, the United States Army investigated classical hallucinogens as incapacitating agents in soldiers, and the United States Central Intelligence Agency conducted clandestine research investigating classical hallucinogens as interrogation agents in which civilians were administered hallucinogens without knowledge or consent. Eventually, both groups ceased to focus on classical hallucinogens in favour of non classical 'hallucinogens' such as the synthetic anticholinergic compound quinuclidinyl benzilate (BZ), which showed greater promise as a warfare agent than LSD because its effects were marked by greater immobility, delirium, amnesia and duration (Lee and Shlain, 1992). Very early academic research on classical hallucinogens was designed without considering the powerful influences of set (psychological state) and setting (environment) (Malitz, *et al.*, 1960; Rinkel, *et al.*, 1960; Hollister, 1961; Rümmele and Gnirss, 1961; Leuner, 1962). Subsequent research, which included more preparation and interpersonal support during the period of drug action, found fewer adverse psychological reactions, such as panic reactions and paranoid episodes, and increased reports of positively valued experiences (Chwelos, *et al.*, 1959; Leary, 1964; Leary, *et al.*, 1963, 1964; Metzner, *et al.*, 1965; Pahnke, 1969).

One major area of early research focused on the comparison of hallucinogen effects with the symptoms of psychosis (e.g. Stockings, 1940; Hoch, *et al.*, 1953; Hoffer and Callbeck, 1960; Leuner, 1962; Kuramochi and Takahashi, 1964). Although the study of hallucinogens as models for the psychosis observed in schizophrenia eventually fell out of favour in psychiatry (Grinspoon and Bakalar, 1979; Snyder, 1988; Strassman, 2001), a renewed interest in this area is emerging, in part due to modern brain imaging techniques and neuropharmacological findings that have supported hallucinogens as a model of at least certain aspects of acute psychosis (Vollenweider, *et al.*, 1997; Gouzoulis Mayfrank, *et al.*, 1998a; Vollenweider and Geyer, 2001; Gouzoulis Mayfrank, *et al.*, 2005, 2006).

Other areas of early human research included investigations of therapeutic applications of hallucinogens in treatment of psychological suffering associated with cancer and in the treatment of substance dependence. Anecdotal observations and non blind studies in cancer patients suffering from anxiety and depression suggested that LSD administration resulted in an ability to openly discuss existential fears and be at peace with approaching death, and that this reorientation often outlasted the acute drug effects (Kast and Collins, 1964; Cohen, 1965; Kast, 1967). Follow up investigations involved the administration of a high dose of a hallucinogen to carefully prepared patients under highly supportive interpersonal conditions, with the patient wearing eyeshades and listening to classical music through headphones during the course of pharmacological action, a model known as 'psychedelic peak therapy' or 'psychedelic therapy' (Kurland, *et al.*, 1969; Pahnke, *et al.*, 1969; Richards, *et al*, 1972; Grof, *et al.*, 1973;

Kurland, *et al*., 1973; Grof and Halifax, 1977; Richards, *et al*., 1977, 1979; Grof, 1980; Richards, 1980; Kurland, 1985). Unfortunately, these early studies did not include the stringent control conditions or groups that now have become standard in modern clinical psychopharmacology research. The results sug gest, however, that these compounds may have improved psychological well being in the face of anxiety and depression secondary to cancer.

Another focus of study was hallucinogen facilitated therapy in the treatment of alcoholism and other forms of substance dependence (e.g. Smart, *et al*., 1966; Hollister, *et al*., 1969; Ludwig, *et al*., 1969; Kurland, *et al*., 1971; Savage and McCabe, 1973). While some studies prepared patients and utilized supportive conditions (e.g. Kurland, *et al*., 1971; Savage and McCabe, 1973), others drastically departed from the 'psychedelic therapy' model (and from the guidelines herein), and involved the administration of high doses to unprepared, restrained patients (e.g. Smart, *et al*., 1966). Results across studies were ultimately inconclusive due to such variations in methods and a lack of modern controls and experimental rigour (Abuzzahab and Anderson, 1971; McGlothlin and Arnold, 1971; Halpern, 1996; Mangini, 1998). Similarly, some therapists reported that hallucinogens administered under supportive contexts could accelerate psychotherapy for a variety of psychological disorders (e.g. Abramson, 1960, 1963; Crochet, *et al*., 1963; Mogar and Aldrich, 1969; Rhead, 1977). However, these reports were largely based on anecdotal clinical accounts rather than con trolled studies.

Escalation in recreational hallucinogen use, primarily LSD, in the 1960s, led to considerable sensationalism concerning these drugs in media coverage. Adding to the controversy was the publicized departure and termination of Timothy Leary and Richard Alpert from Harvard University in 1963 following charges of unorthodox methods in hallucinogen research (Grinspoon and Bakalar, 1979; Lee and Shlain, 1992; Novak, 1997; Strassman, 2001). Leary's subsequent irresponsible advocacy of hallucinogen use by youth further undermined an objective scientific approach to studying these compounds. The growing controversy and sensationalism resulted in increasing restrictions on access to hallucinogens throughout the 1960s (ultimately resulting in the placement of the most popular hallucinogens into Schedule I of the 1970 Controlled Substances Act in the United States), creating substantially greater regulatory barriers for researchers to conduct human trials. The negative publicity also resulted in withdrawal of federal research funds, which had previously supported much of the human research, and in the professional marginalization of clinical investigators interested in pursuing research with hallucinogens. Human research with hallucinogens in the USA became virtually dormant when the last trials were published in the early 1970s. Commenting on the unusual evolution of psychiatric research with hallucinogens, Strassman (2001) mused, "They began as 'wonder drugs,' turned into 'horror drugs,' then became nothing" (p. 28).

Unique risks of human hallucinogen research

Hallucinogen administration in humans results in a unique profile of effects and potential adverse reactions that need to be appropriately addressed to maximize safety. Different risks are associated with different drug classes, and human research with each class requires procedures to be in place to address those particular risks. For example, because high doses of certain opioids and sedative/hypnotics can cause respiratory depression (Gutstein and Akil, 2006; Charney, *et al*., 2006), when conducting research with high doses of these drugs, respiration rate and/or blood oxygen are monitored, and mechanical breathing assistance and appropriate rescue medications are readily available. As another example, administration of high doses of psychomotor stimulants, such as cocaine, can cause cardiac stress (O'Brien, 2006). Therefore, electrocardiogram (ECG) readings taken at screening are scrutinized carefully, pulse and blood pressure are monitored during sessions, and rescue medication for acute hypertension is immediately available. Similarly, human hallucinogen administration entails its own unique risk profile. Unlike opioids, sedative/hypnotics or psychomotor stimulants, the primary safety concerns with hallucinogens are largely psychological rather than physiological in nature.

Physiological toxicity

Hallucinogens generally possess relatively low physiological toxicity, and have not been shown to result in organ damage or neuropsychological deficits (Strassman, 1984; Gable, 1993, 2004; Halpern and Pope, 1999; Hasler, *et al*., 2004; Nichols, 2004; Halpern, *et al*., 2005). Nonhuman animal studies have shown MDMA (structurally similar to some classical halluci nogens, but with a substantially different pharmacological mechanism of action) to have neurotoxic effects at high doses, although MDMA has been judged to be safe for human administration in the context of several therapeutic and basic human research studies. In contrast, there is no evidence of such potential neurotoxic effects with the prototypical classical hallucinogens (i.e. LSD, mescaline and psilocybin). Some physiological symptoms may occur during hallucinogen action, such as dizziness, weakness, tremors, nausea, drowsiness, paraesthesia, blurred vision, dilated pupils and increased tendon reflexes (Isbell, 1959; Hollister, 1961; Nichols, 2004). In addition, hallucinogens can moderately increase pulse and both systolic and diastolic blood pressure (Isbell, 1959; Wolbach, *et al*., 1962b; Strassman and Qualls, 1994; Gouzoulis Mayfrank, *et al*., 1999; Passie, *et al*., 2000; Griffiths, *et al*., 2006). However, these somatic effects vary and are relatively unimpressive even at doses yielding powerful psycho logical effects (perceptual, cognitive and affective) (Metzner, *et al*., 1965; Passie, *et al*., 2000; Metzner, 2004).

Although a full discussion of special physiological toxicity concerns for medical patient populations is beyond the scope of this manuscript, a few observations are worthy of note. The

early literature examining hallucinogens in the treatment of anxiety and depression secondary to cancer indicated that the classical hallucinogens LSD and N,N dipropyltryptamine (DPT) were physiologically well tolerated. The physical adverse effects of these agents observed in cancer patients were manageable and similar to effects observed in physically healthy individuals. These researchers noted that any other symptoms experienced during sessions with cancer patients were symptoms already associated with their existing illness (Richards, *et al*., 1972; Kurland, *et al*., 1973; Kurland, 1985). Early clinical research also safely administered LSD to chronic alcoholics and cancer patients with 'considerable liver dam age', suggesting hepatic concerns are 'negligible unless the dys function is of a critical degree' (Grof, 1980, p. 164).

Participants and review committees may be concerned that LSD or other hallucinogens are associated with chromosomal damage. These concerns stem from an anti LSD media campaign by the USA government in the late 1960s that was based on and followed soon after initial reports (Cohen, *et al*., 1967a,b; Irwin and Egozcue, 1967), suggesting that LSD caused chromosomal damage in human leucocytes (Ott, 1996; Weil, 2004). This campaign included pictures of deformed children (Grinspoon and Bakalar, 1979) at a time when the thalidomide tragedies of a decade earlier were relatively fresh in the public's memory (Ott, 1996). However, many follow up investigations soon squarely refuted the hypothesis that LSD use in humans was a significant risk for chromosomal damage or carcinogenic, mutagenic or teratogenic effects (e.g. Bender and Siva Sankar, 1968; Tjio, *et al*., 1969; Dishotsky, *et al*., 1971; Long, 1972).

Abuse and dependence

Like many classes of psychoactive drugs, hallucinogens are sometimes used in a manner that jeopardizes the safety or well being of the individual or others (e.g. driving while impaired; a pattern of use that interferes with work, school or relationships). Under such circumstances, hallucinogens are said to be 'abused'. However, hallucinogens are not typically considered drugs of dependence in that they do not engender compulsive drug seeking (National Institute on Drug Abuse, 2001, 2006; O'Brien, 2006), consistent with the observation that they are not reliably self administered in nonhuman animals (Poling and Bryceland, 1979; Griffiths, *et al*., 1980; Fantegrossi, *et al*., 2004). Furthermore, they are not associated with a known withdrawal syndrome (O'Brien, 2006). There fore, there is little risk that exposing human volunteers to hallucinogens will leave participants physically or psycho logically dependent on these compounds. This low dependence potential allows for the possibility of administering these compounds to hallucinogen naïve volunteers when blinding issues are critical (e.g. Griffiths, *et al*., 2006). However, in cer tain situations it may be advantageous to study hallucinogen experienced participants (e.g. brain imaging studies requiring the participant to remain immobile).

Acute psychological distress and dangerous behaviour during hallucinogen action

Although hallucinogens have relatively low physiological toxicity and are not associated with compulsive drug seeking, there is still concern that they may pose other psychological risks. The most likely risk associated with hallucinogen administration is commonly known as a 'bad trip' and is characterized by anxiety, fear/panic, dysphoria, and/or paranoia. Distressing effects may be experienced in a variety of modalities: sensory (e.g. frightening illusions), somatic (e.g. disturbing hyperawareness of physiologi cal processes), personal psychological (e.g. troubling thoughts or feelings concerning one's life) and metaphysical (e.g. troubling thoughts or feelings about ultimate evil forces) (McCabe, 1977; Grinspoon and Bakalar, 1979; Strassman, 1984). Because emotional experience is often intensified when under the influence of a hallucinogen, in unprepared individuals or uncontrolled situations any of these effects may potentially escalate to danger ous behaviour. For example, fear and paranoid delusions may lead to erratic and potentially dangerous behaviours, including aggression against self or others (Strassman, 1984). Although very rare, in hazardous and unsupervised conditions, individuals under the influence of hallucinogens have ended their lives by such acts as jumping from buildings (Keeler and Reifler, 1967; Reynolds and Jindrich, 1985; Reitman and Vasilakis, 2004; O'Brien, 2006). We recognize that even under unsupervised and unprepared conditions, reactions to hallucinogens involving violence and self destructive behaviour are rare, and our intention is not to create an unrealistic account of the dangers of hallucino gens. Nonetheless, even infrequent reports of such dangers require that investigators take seriously such risks and take steps to avoid their occurrence.

Prolonged psychosis

Another potential risk of hallucinogen administration is provoking the onset of prolonged psychosis, lasting days or even months (Strassman, 1984). Although determining causa tion is difficult, it appears that individuals who experience such reactions have premorbid mental illness before taking halluci nogens. However, it is unknown whether the precipitation of psychosis in such susceptible individuals represents a psychotic reaction that would have never occurred in the absence of hallucinogen use, or whether it represents an earlier onset of a psychotic break that would have inevitably occurred (Grinspoon and Bakalar, 1979; Strassman, 1984). Unlike acute psychological distress, these cases will be extremely rare in well selected and well prepared participants. In a survey of investigators who had administered LSD or mescaline, Cohen (1960) reported that only a single case of a psychotic reaction lasting more than 48 h occurred in 1200 experimental (non patient) research participants (a rate of 0.8 per 1000). Notably, the individual was an identical twin of a schizophrenic patient and thus would have been excluded under the proposed guide lines. Prolonged reactions over 48 h were slightly more frequent

in patients undergoing psychotherapy than in experimental non patient participants, but still relatively rare, occurring at a rate of 1.8 prolonged reactions per 1000 patients. Cohen (1960) also reported that suicide attempts and completed suicides occurred at a rate of 1.2 and 0.4, respectively, per 1000 patients. The causal link between hallucinogen exposure and suicide or suicide attempt was only clear for a portion of these cases in patients, and no suicides or suicide attempts were noted for the 1200 non patient, experimental participants. However, it is important when evaluating these data to con sider that only 44 of the 62 researchers queried by Cohen returned survey results (Cohen, 1960; Novak, 1997). Although Cohen and Ditman (1962) subsequently expressed misgivings over the increased incidence of adverse effects due to the increasing recreational use of LSD and some questionable clin ical practices, they maintained that when used under the proper guidelines, LSD was an important tool for use in human research (cf. Novak, 1997). McGlothlin and Arnold (1971) reported one case out of 247 individuals who received LSD in either experimental or psychotherapeutic studies in which an LSD related psychotic reaction lasting more than 48 h occurred. That single case was a patient who received repeated LSD administrations in a psychotherapeutic context. Although very rare, care must be taken to minimize the risks of such an episode. The volunteer selection guidelines, addressed in a later section, will be the key factor in minimizing the risk of pro longed psychosis in human hallucinogen research studies.

Some clinical observations suggest the possibility that unconscious psychological material may be activated during hallucinogen sessions, and that such material, if not properly worked through and psychologically integrated, may lead to psychological difficulties of a non psychotic nature, such as negative emotions and psychosomatic symptoms, lasting beyond the session (e.g. McCabe, 1977; Grof, 1980). Although these observations have not been examined experimentally, they deserve consideration. As suggested in our subsequent discussion of volunteer monitor interactions, we believe that the strong interpersonal support from session monitors before, during and following sessions will minimize any enduring untoward psychological effects.

Lasting perceptual abnormalities

Another potential risk of hallucinogen administration is hallu cinogen persisting perception disorder (HPPD). In order to meet DSM IV TR criteria for this disorder, a hallucinogen user must re experience perceptual effects similar to those expe rienced under acute hallucinogen action after cessation of hallucinogen use, these effects must be clinically distressing or impair functioning, and the effects must not be caused by a medical condition or be better explained by another psychiatric disorder or hypnopompic hallucinations (American Psychiatric Association, 2000). The incidence of HPPD is unknown, although it is thought to be very uncommon given the rela tively few cases reported out of the millions of hallucinogen doses consumed since the 1960s (Halpern and Pope, 2003). Although the term 'flashback' is sometimes used interchange ably with HPPD, the former term is often used to describe any brief perceptual effects reminiscent of acute hallucinogen effects but occurring beyond acute hallucinogen use, usually in the absence of clinical distress or impairment (Lerner, *et al*., 2002). Indeed, many illicit hallucinogen users report some brief visual abnormalities occurring after acute hallucino gen effects, but only for a small minority of users are these effects troubling or impairing enough to be considered clini cally significant or warrant the diagnosis of HPPD (Lerner, *et al*., 2002; Baggott, *et al*., 2006). Many illicit users regard such sub clinical effects as benign and pleasurable (Strassman, 1984; Lerner, *et al*., 2002; Frecska and Luna, 2006). Impor tantly, the incidence of HPPD or other perceptual abnormali ties appears to be much lower in therapeutic or research contexts with careful screening and preparation than in the context of illicit recreational use, which may include the con founds of polydrug use and unscreened psychiatric disorders (Cohen, 1960; McGlothlin and Arnold, 1971; Strassman, 1984; Halpern and Pope, 2003). Because such perceptual abnormalities are poorly understood, researchers administering hallucinogens to human volunteers should probe for perceptual disturbances in follow up contact.

Guidelines for safety

The guidelines that follow are intended to support the safe administration of high doses of hallucinogens to human volun teers while minimizing potential adverse reactions. Although a previous paper outlined methodological issues relevant to the study of hallucinogens in humans (Gouzoulis Mayfrank, *et al*., 1998b), safety issues were not the primary focus of that paper. The present paper substantially complements this previ ous work by providing a more detailed discussion of safety concerns. Issues relevant to the conduct of human research with drugs of abuse in general have been well described (Fischman and Johanson, 1998). The present guidelines extend and complement the recommendations of Fischman and Johanson (1998) for high dose hallucinogen research. For some domains, such as volunteer selection, volunteer prepara tion, and the interactions between the volunteer and study personnel, the proposed criteria are substantially more exten sive than those presented by Fischman and Johanson (1998) and those routinely used in human behavioural pharmacology because these domains appear to require even greater attention for hallucinogens than for other classes of psychoactive drugs. Although particular aspects of the proposed guidelines may be debatable, it is hoped that this paper will encourage such dis cussion while conveying the general themes and major domains of concern in human hallucinogen research. The proposed guidelines may serve as a helpful starting point for investiga tors planning to conduct human hallucinogen research.

Selection of volunteers

There are two main domains of consideration for volunteer selection. First, selection criteria may be methodological in nature and involve the specific research questions being explored. Second, which is the focus of this manuscript, is safety related selection criteria. In our studies at Johns Hopkins, participants must be in good general health as assessed by detailed medical history, physical examination, 12 lead ECG, blood chemistry profile, haematology and urinalysis. Pregnant women or those not practicing effective means of birth control are excluded. Relevant to general medical screening, classical hallucinogens moderately increase pulse and both systolic and diastolic blood pressure (Isbell, 1959; Wolbach, *et al.*, 1962b; Strassman and Qualls, 1994; Gouzoulis Mayfrank, *et al.*, 1999; Passie, *et al.*, 2000; Griffiths, *et al.*, 2006). Therefore in our studies of psilocybin to date, volunteers have been excluded if resting blood pressure exceeded 140 systolic and 90 diastolic (mmHg), averaged across four assessments on at least two separate days. Using these screening parameters with 54 participants to date, no psilocybin session has resulted in blood pressure increases considered medically dangerous, and we have never needed to administer an anti hypertensive medication in response to psilocybin effects. Modification of these limits may be considered in future studies if safety continues to be observed under these parameters.

Certain medications may alter the effects of a hallucinogen and, therefore, individuals taking these medications should be excluded from participation. Specifically, chronic administration of tricyclic antidepressants and lithium (Bonson and Murphy, 1996), and acute administration of serotonin reuptake inhibitors (Fiorella, *et al.*, 1996) and the antipsychotic medication haloperidol (Vollenweider, *et al.*, 1998) have been shown to potentiate hallucinogen effects, and therefore participants' use of these represents a safety concern. Chronic administration of serotonin reuptake inhibitors (Stolz, *et al.*, 1983; Strassman, 1992; Bonson, *et al.*, 1996) and monoamine oxidase inhibitors (Bonson and Murphy, 1996) have been shown to decrease sensitivity to hallucinogens, and therefore participants' use of these represents a scientific concern. We also advise investigators to include questions concerning over the counter dietary supplements in addition to prescription medications when probing medication history, and to exclude those taking potentially problematic substances (e.g. 5 hydroxytryptophan and St John's Wort may affect serotonergic function, and, therefore, it is appropriate to exclude individuals currently or recently taking these products). It should also be noted that administration of *ayahuasca* (which contains monoamine oxidase inhibitors in addition to DMT) to individuals taking serotonin reuptake inhibitors may lead to a severe serotonin syndrome reaction (Callaway and Grob, 1998).

Psychiatric screening criteria are important for minimizing the already low chances of precipitating a longer term psychotic reaction by hallucinogen administration. Thorough psychiatric interviews (e.g. SCID; First, *et al.*, 2001) should be conducted to identify contraindicated psychological functioning or history. In our research, individuals are excluded who have a current or past history of meeting DSM IV criteria for schizophrenia or other psychotic disorders (unless substance induced or due to a medical condition), or bipolar I or II disorder, which are the most important conditions to exclude for ensuring safety. We also exclude those with a first or second degree relative with these disorders. There is considerable evidence from family, twin and adoptive studies that genetic factors make a robust contribution to the aetiology of schizophrenia, with genetic factors established as relevant to some, perhaps all cases (Buchanan and Carpenter, 2005). In fact, data indicate that there is approximately a six fold greater chance of developing schizophrenia in second degree relatives of individuals with schizophrenia (Patel, *et al.*, 2003). Other investigators have also excluded individuals scoring high on the personality traits of rigidity and emotional lability on the grounds that these have been significantly associated with negative experiences during hallucinogen action and during non pharmacologically induced altered states of consciousness (Dittrich, 1993; Hasler, *et al.*, 2004).

Depending on the nature of the study, it may be appropriate to exclude those with other psychiatric disorders as well. Unless the research study is designed to specifically address a question relevant to a specific psychiatric disorder, our advice is to select a population that is psychiatrically healthy. This strategy is warranted because the effects of hallucinogens may potentially interact with various psychiatric disorders. Furthermore, including volunteers with psychiatric disorders may increase the chances that symptoms from such disorders may inadvertently be misattributed to hallucinogen action. For example, our recent studies with healthy volunteers have excluded volunteers with a current or a recent past history (e.g. within the last 5 years) of alcohol or drug dependence (excluding caffeine and nicotine) or major depression, and volunteers with current obsessive compulsive disorder, dysthymic disorder, panic disorder, dissociative disorder, anorexia nervosa or bulimia nervosa.

Recent and current studies have investigated therapeutic applications of psilocybin for psychiatric disorders (Grob, 2005; Moreno, *et al.*, 2006). Because preliminary reports have suggested safety, studies examining therapeutic indications are likely to continue. These studies target for participation volunteers with disorders that would normally be excluded from non treatment studies. Therefore, additional considerations are appropriate for such studies. For example, in a study of hallucinogen assisted therapy for depression or anxiety, individuals should be excluded whose symptoms of depression or anxiety are sufficiently severe to warrant immediate treatment with medication (e.g. due to suicidal ideation). In addition, clinical treatment studies may choose to lift restrictions on relatively minor non target psychiatric disorders that would be excluded in studies with healthy volunteers. For example, a study of hallucinogens in the treatment of anxiety related to cancer might choose to allow the inclusion those with comorbid dysthymic disorder or mild obsessive compulsive disorder. Investigators should examine the relevant evidence when considering lifting specific exclusions, proceed cautiously, and implement any supplemental safeguards that might be appropriate for such exceptions.

Study personnel

It is difficult to overemphasize the importance of the interpersonal atmosphere created by study staff in influencing a volunteer's response to a hallucinogen. Most critically, this applies to the interpersonal environment created by the actual session monitors (Leary, *et al*., 1964; Masters and Houston, 1966). We use the term 'monitor' to refer to the staff members, who will be with the participant in the session room during the course of hallucinogen action. The monitors should be knowledgeable about the medical and psychological markers of potential adverse reactions to the drug. Furthermore, monitors should have significant human relation skills and be familiar with descriptions of altered states of consciousness induced by hallucinogens. Personal experience with techniques such as meditation, yoga or breathing exercises may also prove to be helpful in facilitating empathy for volunteers who experience altered states of consciousness during hallucinogen action. The lead monitor for each participant in the Johns Hopkins studies to date has been a clinical psychologist or a clinical social worker. However, we believe that clinical sensitivity (e.g. empathy, respect) is likely more important than formal degrees when considering monitor qualifications.

We recommend the presence of at least two monitors during hallucinogen administration sessions so that the volunteer will never be alone should one monitor need to briefly leave the session room (e.g. to the restroom). For each participant in the Johns Hopkins studies, we have specified a primary monitor (who takes the lead in participant interactions) and an assistant monitor, with differing required levels of involvement for the two monitors during volunteer preparation (see Preparation of volunteers section below). In prior research into potential treatment applications of hallucinogens, the presence of both genders in the monitoring team has been recommended (Grof and Halifax, 1977; Grof, 1980; Kurland, 1985). Having both genders present may foster feelings of security. In the Johns Hopkins studies, we have followed this recommendation when possible, but also have conducted sessions in which the primary and assistant monitors were of the same gender as the volunteer. We would counsel against both members of the monitoring team being the opposite gender of a volunteer, unless there is a staff member of volunteer's gender who has established some rapport with the volunteer in advance, and who can quickly be summoned to assist should support be needed in the restroom. For studies that are intended to maximize the potential for mystical type experience during hallucinogen administration, an additional valuable monitor characteristic may be her or his ability to interact with and relate to the participant concerning spiritual issues (e.g. Moss and Dobson, 2006; Council on Spiritual Practices, 2001).

Although the volunteer's interactions with the monitors are of paramount importance, all individuals at the study site having contact with the volunteer on or before the session day may influence a volunteer's reaction to a hallucinogen. Pre session negative mood consisting of anxiety or depression has been shown to significantly predict anxious or other negative experiences during the session (Metzner, *et al*., 1965). Strassman (2001) reported that a visiting medical student's unexpected interaction with a volunteer before the session may have contributed to an adverse event resulting in the volunteer leaving the study site under the influence of psilocybin. To the degree possible, investigators should work with all personnel that the volunteer may encounter (e.g. receptionist, building security, nurses) to ensure that volunteers are treated with courtesy and respect. For example, in the Johns Hopkins studies, a research staff member other than the study monitors meets with the volunteer in the morning and administers a few pre session questionnaires and manages other logistics. This staff member should be friendly, welcoming and compassionate, as he or she inquires as to the volunteer's current emotional and physical well being (e.g. recent sleeping history, interpersonal or work stressors, anticipation of session, adherence to study dietary and medication/drug restrictions). The staff member should maintain a positive social rapport with the volunteer to reduce the likelihood of adverse psychological reactions during the session and to gain accurate information on the volunteer's condition so that other study staff may be notified if there is any potential reason to postpone or cancel the session (e.g. if the volunteer is experiencing a particularly stressful life event or is feeling ill). If any staff member treats the volunteer disrespectfully or coldly (i.e. 'like a guinea pig'), this may negatively influence the volunteer's psychological state and subsequent hallucinogen experience. We recognize that treating volunteers respectfully is an ethical imperative for all human research. However, with hallucinogen administration research, the importance of this mandate is even more compelling given the powerful influence of set and setting on hallucinogen effects. Therefore, we recommend providing additional attention to volunteer rapport beyond what is customary in general human behavioural pharmacology practice.

Physical environment

The physical environment during hallucinogen sessions is extremely important for ensuring safety for volunteers in two respects. First, an aesthetically pleasing environment may decrease the probability of acute psychological distress. The Johns Hopkins hallucinogen research projects use a living room like setting (Figure 1). The furniture is comfortable and is atypical for a research laboratory or medical office setting. An overly 'clinical' environment with an 'antiseptic' look (e.g. white walls, extraneous medical equipment, personnel in white lab coats) may increase anxious reactions. Strassman (2001) noted that the medically oriented environment in which his DMT studies were conducted may have contributed to volunteers having unpleasant subjective experiences. For example, some volunteers reported vivid and realistic experiences of being medically examined by extraterrestrials. It has also been noted that many of the potentially unpleasant physical reactions to hallucinogens (e.g. subjective changes in temperature, difficulty in breathing, various bodily sensations) might be in part psychosomatic in nature (Blewett and Chwelos, 1959),

Figure 1 The living room like session room used in the Johns Hopkins hallucinogen research studies. Aesthetically pleasing environments such as this, free of extraneous medical or research equipment, in combination with careful volunteer screening, volunteer preparation and interpersonal support from two or more trained monitors, may help to minimize the probability of acute psychological distress during hallucinogen studies. For studies that investigate potential therapeutic effects or the phenomenology of introspective hallucinogen experiences, the use of eyeshades and headphones (through which supportive music is played) may contribute to safety by reducing the distractions of environmental stimuli and social pressures to verbally interact with research personnel.

and therefore possibly more likely in settings evocative of med ical conditions (Masters and Houston, 1966). Some protocols may require videotaping of sessions for scientific purposes. Although there might be concern that videotaping could increase self consciousness or paranoia, we have no evidence that this has occurred in the Johns Hopkins studies, in which videotaping of sessions is routine.

Beyond the psychological importance of a comfortable, relaxing environment, attention must be paid to the physical safety of the environment. The environment should be designed keeping in mind the perceptual changes and disorientation that can occur under the influence of hallucinogens. Thus, any potentially dangerous objects (e.g. furniture with sharp corners; glass lamps) should be avoided. If there is a window in the room, the investigators need to be confident that the volunteer could not exit the window if in a delusional state. Additionally, the session room should not have a telephone, and the partici pant should surrender her or his cellular telephone before the session. Not only may an incoming telephone call be distract ing or alarming while under the influence of a hallucinogen, but it may also represent a safety risk, as Strassman (2001) has reported a case in which a participant used a session room telephone to call a companion, which culminated in the two fleeing the study site. Having a private restroom located near the session room would be ideal for volunteer use during the session. A shared restroom may be used if the monitors ensure that the volunteer does not interact with non study personnel while going to the restroom (more details under the section: *Conduct of hallucinogen administration sessions*). Of course, most research laboratories do not provide the ideal physical environment. Thus, resourcefulness and ingenuity may be necessary to convert a less than ideal location into a relaxing and secure environment.

Preparation of volunteers

As with any human research with psychoactive drugs, volun teer preparation at the earliest stages must include a thorough review of the consent form, which should include in plain language the range of experiences that may result from halluci nogen administration, including changes in perception, sense of time and space, and emotion (possibly including anxiety, fear, panic and paranoia). Relative to other drug classes, the subjec tive effects of hallucinogens are likely more difficult to describe to a naïve volunteer; therefore, additional time may be neces sary to fully discuss these potential effects with volunteers. The consent form should also include the approximate timecourse of the drug, the state of knowledge concerning its toxicity pro file, and its status as an experimental drug. In addition, the consent form should state that there is a relatively small risk of adverse effects that last for hours to days after the hallucino gen session. These include mood disorders (such as depression), psychotic disorders and anxiety disorders. It should also state that there are rare reports in which hallucinogen exposure appears to cause, accelerate or precipitate the onset of signifi cant or lasting psychiatric illnesses such as psychoses and intermittent or persisting visual perceptual abnormalities ('flashbacks', HPPD).

The next step in volunteer preparation is to conduct a series of meetings between the monitors and volunteer to build rapport and trust. The relationship between the monitors and the volunteers should be well established by the time of the first session (Masters and Houston, 1966). In the Johns Hopkins studies, there are at least eight contact hours over the course of at least four meetings, usually over a 1 month period. One

of these preparatory meetings should be conducted in the room in which the hallucinogen is to be administered, to familiarize the participant with the physical environment. The primary monitor meets with the volunteer during all of these meetings, while the assistant monitor is required to be present on at least one occasion. It is important that the assistant monitor, in addition to the primary monitor, has developed a trusting relationship with the volunteer because this assistant monitor will be the only person in the session room with the volunteer if the primary monitor needs to leave briefly.

During these preparatory meetings, the monitors discuss meaningful aspects of the volunteer's life. The main purpose of the participant monitor meetings is to develop rapport and trust, which we believe helps minimize the risk of fear or anxi ety reactions during the hallucinogen session. This typically includes discussions of the volunteer's childhood, romantic life, current relationships with family and friends, and the volunteer's philosophical and/or spiritual beliefs. Reviewing personal history and feelings may be important for two rea sons. First, this discussion helps establish a significant level of trust. The interaction should convey that all aspects of the per son are welcome, from the petty to the noble, from embarrass ments to achievements and from sorrow to joy. By the time of the hallucinogen session day, the volunteer will ideally feel completely comfortable with the monitors, reducing the likeli hood of paranoia (e.g. feeling that the monitors are trying to control her or his mind, or have deceived the volunteer about the nature of the study). Second, related personal material may 'emerge' under the effects of the hallucinogen. That is, the vol unteer may experience intense thoughts, feelings and visions related to his or her personal history or world view. Knowing about the volunteer's life will allow the monitors to better understand her or his session experience and help the monitors in providing interpersonal support should strong emotions arise. If it is felt that sufficient rapport and trust have not developed during these monitor meetings, then either addi tional contact hours should be provided, or the volunteer's par ticipation should be cancelled. A high dose of a hallucinogen should not be administered to a volunteer if sufficient trust has not been established. As with other forms of human research involving the development of rapport and trust (e.g. clinical trials involving psychotherapy), investigators should be careful that this rapport and trust does not create a situation in which the volunteer feels obligated to remain in the study. Volunteers and monitors should be clear that participation is voluntary, and that the participant will be fully supported if her or his decision is to quit the study.

At some point during preparatory meetings, time must be devoted to explain the study logistics. These should include the timing of the session (e.g. what time to arrive at the labora tory if an outpatient study, what time the session is likely to end), any restrictions on diet or contraindicated medicines, drugs or nutritional supplements (e.g. if fasting or a low fat diet is required the morning before session), and any require ments of other people (e.g. if a family member or friend is to pick up the participant at the end of the session).

This discussion should also include thorough descriptions of study procedures, to the degree allowable by blinding issues. For example, if cognitive or memory tests are to be performed, or questionnaires are to be answered, the participants should be aware of these requirements. If physiological measures, such as blood pressure, are to be taken during the time of drug action, this also should be explained. The activities during hallucinogen action will naturally depend on the scientific questions under investigation. Whatever the nature of the experiment after hallucinogen administration, the scenario should be thoroughly discussed with the volunteer in prepara tion. In some cases, such as with brain imaging research, it may be helpful for volunteers to be run through a preliminary research session to familiarize them with the equipment and procedures. Some studies have conducted an initial non blind hallucinogen administration session in which safety measures are assessed before subsequent blinded sessions to, among other reasons, acquaint volunteers with the effects of the drug before the introduction of additional, potentially anxiety pro voking measures (e.g. blood draws) (Strassman and Qualls, 1994; Strassman, *et al*., 1994, 1996).

The preparation of the volunteer should involve a detailed discussion of the possible range of experiences that may be encountered after hallucinogen administration. This includes the typical onset and duration of the drug(s) under investiga tion. Preparation involves discussion of the various potential physical sensations, such as nausea or heightened awareness of physiological processes, such as breathing and heartbeat. Volunteers are encouraged to trust that their bodies will continue to function properly regardless of such sensations, and that these bodily processes will continue without the volunteers' volitional control.

The major categories of potential psychological experiences during hallucinogen action should be discussed with the partic ipant. The range of subjective experience under hallucinogens can be remarkably broad (Blewett and Chwelos, 1959; Richards, 1980; Masters and Houston, 1966; Strassman, 2001; Nichols, 2004; Stolaroff, 2004). This range of experiences includes perceptual changes, such as visual illusions, intensifi cation of colours, proprioceptive changes (e.g. one's body may feel gigantic or tiny), and synesthesia (e.g. seeing sounds or hearing colours). Another type of possible experience is the alteration of emotions, such that emotions of either a positive or negative nature may be greatly intensified, yielding experi ences that may range from euphoria to despair. Another cate gory of possible effects involves changes in the sense of time and space. At the extremes, time and/or space may be experi enced as infinite or nonexistent. Other experiences may include thoughts, feelings or insights concerning one's personal history (e.g. revisiting childhood memories) or current life circum stances (e.g. relations with loved ones), highly symbolic experi ences (e.g. involving religious symbols, animals, etc.), and experiences described by some to be of a mystical or spiritual nature. Importantly, it should be emphasized that these experi ences may consist of much more than the participant subjec tively observing internal and external events. Rather, the effects

may involve a profound change in one's sense of self, such that one feels as if he or she is merging into the surrounding environment or the entire universe (Schultes, *et al*., 2001). The individual may temporarily experience a complete loss of subjective self identity, a phenomenon sometimes referred to as 'ego loss' or 'ego death' (e.g. Leary, *et al*., 1964; Grof and Halifax, 1977; Grof, 1980). While a detailed discussion con cerning the range of possible hallucinogen effects will enhance safety by psychologically preparing the participant for the unique and often intense effects of a hallucinogen, it may also serve to undermine the blind. That is, such preparation may train the participant on how to identify a hallucinogen by its effects. Nonetheless, the primary concern must be the parti cipant's safety. Therefore, researchers must minimize the potential for unblinding by manipulating other aspects of the experimental design, such using hallucinogen naïve participants or the use of an active placebo (e.g. Griffiths, *et al*., 2006).

The volunteers should be given guidance on how to handle difficult hallucinogen experiences. Whether the disturbance consists of frightening illusions or internal imagery, difficult thoughts and feelings about some past or present personal issue, or anxiety related to a radical change in sense of self (e.g. temporary loss of self identity), the volunteer is encour aged to mentally surrender to the experience, trusting that her or his usual state of consciousness will return when the drug effects resolve (Blewett and Chwelos, 1959; Masters and Houston, 1966; McCabe, 1977). For example, if the participant experiences disturbing internal imagery of a demon or monster, he or she is encouraged to mentally approach the figure and interact with it (e.g. imagine asking the figure why it has appeared), rather than attempt to flee from the disturbing imagery. The participant should be alerted that sometimes people experience extremely convincing sensations of dissolv ing, melting, exploding and so forth, and that the best way to deal with all such situations is to surrender to the experience, subjectively allowing oneself to dissolve, melt or explode. Simi lar advice applies to physical symptoms such as nausea; for example, participants may be encouraged to 'dive in' to their stomachs, which may alleviate the nausea, as it has been sug gested anecdotally that nausea and other somatic discomforts may in part be of a psychosomatic nature (Blewett and Chwelos, 1959; Masters and Houston, 1966).

The preparation of volunteers for hallucinogen administra tion will require balancing the ethical requirements to prepare the volunteer for the potentially powerful psychological effects of hallucinogens, with the scientific concern not to bias the volunteer with respect to the dependent variables. This is especially true because classical hallucinogens have been shown to increase suggestibility in an experimental model involving body sway (Sjoberg and Hollister, 1965; Middlefell, 1967), and suggestibility has been proposed as a potential mechanism of the possible therapeutic efficacy of hallucinogens (Dobkin de Rios, *et al*., 2002; Barbosa, *et al*., 2005). That is, one could argue that examples conveyed during preparation are then experienced during the session only due to an increased level of suggestibility during hallucinogen action. Increased suggestibility would seem to be of greatest concern as a confound when investigating the phenomenology of sub jective hallucinogen occasioned experience (e.g. the study by Griffiths, *et al*. (2006), demonstrating that psilocybin can occa sion mystical type experiences under supportive conditions). In the study by Griffiths, *et al*. (2006), although experiences of a spiritual variety were included among the range of possible effects conveyed in preparation, the monitors emphasized that these experiences were not the only variety of interesting or valuable effects that might occur. Specific categories of mystical type experience to be assessed in measures were not discussed. In the Johns Hopkins studies, we have not encouraged participants to read the diverse and widely varying published accounts of hallucinogen effects as part of their preparation, because this may introduce compelling idiosyncratic expecta tions. Our research has proceeded safely by delivering all such preparatory information to participants verbally during pre session meetings with monitors. Researchers will need to design studies such that a maximum amount of preparation is provided for safety reasons, while not confounding the particular hypothe ses being studied. Furthermore, controlled studies should ensure that the unique preparation methods and research environment qualities described herein are in place, under double blind condi tions, for both hallucinogen and placebo groups (or conditions). For example, in the study by Griffiths, *et al*. (2006), the use of identical procedures under double blind conditions for psilocybin sessions and the active placebo (a high dose of methylphenidate) sessions permitted a reasonable degree of control over suggestibility.

Conduct of hallucinogen administration sessions

As with research with many other psychoactive drugs, a physi cian should be available during hallucinogen sessions, should any untoward medical complications arise. Furthermore, med ication for the treatment of acute hypertension (e.g. intrave nous labetalol) should be immediately available in the event that blood pressure exceeds predetermined safety parameters.

Adverse psychological reactions to hallucinogens will be minimized when studies are conducted under conditions that provide strong interpersonal support to the participants (Blewett and Chwelos, 1959; Chwelos, *et al*., 1959; Pahnke, 1969; Masters and Houston, 1966). The monitors should care fully observe the participant and be vigilant for signs of psy chological distress. If the volunteer needs to walk to complete study tasks or to go to the rest room, the monitors should stand close by to assist by gently holding an arm or shoulder. Even with high doses of hallucinogens, individuals do not typically show substantial motor impairment, and will likely be able to ambulate without considerable difficulty (with the exception of hallucinogens such as parenteral DMT with abrupt effects and short duration of action). However, perceptual and propri oceptive effects may make walking disorienting, which is why gentle guidance may be helpful. One of the monitors should always be present in the session room with the participant. Because the session monitors will have developed rapport and

trust with the participant, they should be the only people to interact with the volunteer during the course of hallucinogen action, barring any non routine event (e.g. fire alarm, medical intervention by a specialist). Individuals who are anticipated to have contact with the volunteer during the course of hallucinogen action (e.g. nurse, physician) should have at least met with the volunteer once prior to session to develop some degree of rapport and trust.

For all but the shortest acting hallucinogens (e.g. parenteral DMT), the participant is likely to need to use the restroom at some point while experiencing hallucinogen effects. If a private restroom is not available, then study staff should escort the volunteer to assure that no one is in the restroom. Either the restroom door needs to have no lock, or study staff should have a key readily available if needed. Cohen (1960) reported a case in which a depressed patient who had been administered LSD barricaded himself into a room to attempt suicide. In the Johns Hopkins studies, sessions are conducted in a room located on the third floor of a research facility. The session room itself has a private restroom just outside of the session room. During sessions, the volunteer is closely escorted to the restroom and a session monitor waits just outside the restroom to be available if the volunteer should encounter any difficulties. Furthermore, waiting in this area outside the restroom allows the monitors to ensure that the volunteer does not exit the research site. Any attempt by a disoriented volunteer to leave the session area would be met with compassionate but firm direction to return to the session room.

Serious attention must be devoted to the possibility of volunteers trying to leave the study site under the influence of a hallucinogen. Walter Pahnke's (1963) dissertation study (known as the 'Good Friday Experiment') examined the ability of a high dose of psilocybin to occasion mystical experiences by administering either psilocybin or placebo (randomly assigned) to seminary students in a small, basement chapel into which a Good Friday service from the main sanctuary was broadcast. A retrospective investigation conducted over 25 years after the original experiment revealed that two volunteers left the chapel under the influence of psilocybin (Doblin, 1991). One of these volunteers reported feeling imprisoned in the chapel and left the chapel during a portion of the experiment. The other volunteer abruptly left the chapel believing that God had chosen him to immediately announce to the world the dawning of an age of peace (Roberts and Jesse, 1997; Smith, 2000). This volunteer was apprehended by the research staff and administered the antipsychotic agent chlorpromazine after efforts to calm him were unsuccessful (Doblin, 1991; Roberts and Jesse, 1997; Smith, 2000). Strassman (2001) also reported an incident in which a participant experiencing the full effects of a high dose of psilocybin evaded the research staff and left the research site. Fortunately, the participant's spouse monitored the participant and no one was injured.

The risks of allowing a research volunteer experiencing the effects of a hallucinogen to leave the study site are significant. For example, in a bewildered or delusional state, the person might walk into traffic or attempt to drive. Although many hallucinogen users maintain reasonable control while under the influence of hallucinogens, panic or delusional reactions to hallucinogens have in rare circumstances resulted in tragic consequences, such as jumping out of windows (Keeler and Reifler, 1967; Reynolds and Jindrich, 1985; Reitman and Vasilakis, 2004; O'Brien, 2006). Interestingly, the volunteer who fled Strassman's (2001) study site on psilocybin was a carefully screened, experienced LSD user. Therefore, it is imperative for safety reasons that the study site environment, session procedures and participant preparation all minimize the chance of a volunteer leaving the study site.

Strategies for handling non routine scenarios should be considered. For example, how are study monitors and the volunteer expected to respond in the event of a fire alarm or fire? On the single occasion at Johns Hopkins in which a fire alarm sounded during a session, the two study monitors closely escorted the volunteer outside, making sure to minimize contact with other individuals. The three of them walked to a nearby quiet area with an attractive landscape and enjoyed the scenery until the volunteer and monitors could return to the building. The monitors encouraged the participant to view the occasion as an opportunity to enjoy the natural world outdoors (something normally unavailable during sessions), rather than as an impediment to having a successful session. If any non routine events occur, the monitors should maintain contact with the volunteer throughout.

If participants become anxious during the course of hallucinogen action, it is now widely recognized that the appropriate first response is to provide strong personal support and reassurance (O'Brien, 2006). This primarily includes interacting with the volunteer in a comforting and reassuring manner. If the volunteer is behaving anxiously and a negative psychological reaction seems to be escalating, the monitors should convey a solid sense of security and calm, while empathizing with what may be an incredibly intense and unpleasant experience. Attempts to 'talk down' the participant (i.e. the use of reality defining techniques to distract the participant from or attenuate the altered state of consciousness) may be counterproductive and aggravate a difficult reaction (McCabe, 1977). Instead, participants should be reminded to surrender to the experience. Appropriate forms of reassurance may include a supportive touch to the arm or shoulder with verbal reminders that the participant is in a research study, has taken the hallucinogen, and that he or she will return to normal consciousness in 'a few minutes' or 'a few hours' (or whatever the appropriate estimate may be, depending on the specific drug under study and when it was administered). During an intense hallucinogen occasioned experience when verbal interactions may be of limited help, a powerful form of reassurance (sometimes called 'interpersonal grounding') is simply holding the hand of the participant (McCabe, 1977). Many volunteers report that during such experiences, a reassuring hand provides an incredible sense of stability and connection. Monitors should demonstrate this practice during preparation to normalize hand holding during sessions.

If volunteers have been appropriately screened and the guidelines herein followed, reassurance should be sufficient to diffuse acute psychological distress in the vast majority of cases. For example, in recent studies in our laboratory, in which we have administered high doses of psilocybin to 54 volunteers, reassurance has been sufficient to handle all cases of acute psychological distress that have arisen. Although pharmacological intervention is a last resort and should rarely, if ever, be needed, medications should be readily available for use if the need arise. For cases in which acute psychological distress is insufficiently managed with reassurance alone, treatment with a benzodiazepine anxiolytic is the pharmacological intervention of choice (Abraham and Aldridge, 1993; Frecska and Luna, 2006; O'Brien, 2006). In these cases, we recommend a 10 mg oral dose of diazepam (Grinspoon and Bakalar, 1979), although oral doses of 15 30 mg per hour or every few hours as needed have been recommended for pharmacological treatment of 'bad trips' that do not respond to reassurance in emergency department settings (Ungerleider and Frank, 1976). Because of its high lipid solubility, diazepam has a more rapid onset, a shorter time until peak plasma concentration and a shorter duration of therapeutic action than many other benzodiazepines including lorazepam, despite the fact that lorazepam has a shorter elimination half life (Greenblatt and Shader, 1985; Funderburk, *et al.*, 1988). Although the intravenous route may be considered, the oral route is preferable because intravenous injection procedures may further exacerbate the participant's anxiety. Moreover, antipsychotic medications (e.g. risperidone, olanzapine) should be available in the event that an adverse reaction escalates to unmanageable psychosis. However, experienced clinicians have suggested that although antipsychotic medications may reduce psychotic behaviour through sedation, their use may be problematic because the effects may be abrupt, unpleasant and intense and their use may result in subsequent psychological problems (McCabe, 1977; Grinspoon and Bakalar, 1979; Grof, 1980). Furthermore, pretreatment with the antipsychotic haloperidol has been shown to exacerbate the psychosis like effects of psilocybin (Vollenweider, *et al.*, 1998), suggesting that haloperidol should not be used as a rescue medication. Although not approved for use in the USA, ketanserin (a 5 HT_{2A} antagonist) pretreatment has been shown to attenuate psilocybin effects (Vollenweider, *et al.*, 1998), suggesting possible use as a rescue medication for hallucinogen administration. Ultimately the decision to medicate will depend on whether the monitors and responsible physician judge that they are capable of maintaining the safety of the volunteer and others without medical intervention. Bringing the participant to the emergency department represents an ultimate 'last resort' in the treatment of a very difficult (i.e. psychotic) reaction. However, medical evaluation by well meaning emergency department personnel, who are inexperienced with hallucinogen effects can readily escalate and prolong an adverse reaction. Therefore, all possible efforts should be made to treat a difficult experience in the session context, even if pharmacological intervention is required.

The conduct of the session will largely be based on the particular research topics being studied. The research requirements of many types of studies will require the participants to adhere to regimented testing conditions (e.g. cognitive tests, memory tests, brain scans). In such investigations, interference with procedures may be minimized by judiciously selecting dose and the hallucinogen experience level required of volunteers. Adverse reactions will generally be more likely at higher hallucinogen doses; however, adverse reactions can potentially occur at any dose level. Experienced hallucinogen users may be particularly appropriate participants for studies involving challenging conditions, such as remaining immobile for long periods in a confining brain imaging scanner. Regardless of experience level and dose, however, the possibility of psychological adverse reactions exists whenever a hallucinogen is administered. To the degree possible, investigators should attempt to implement their scientific protocols as planned. However, monitors should always be vigilant for potential adverse psychological reactions. In the event of a significant adverse psychological reaction, interpersonal support should be provided even if it interferes with data collection. Clearly, volunteer safety must take priority over scientific procedures. In studies such as ours, in which participants are encouraged to focus their attention inward by wearing eyeshades and listening to music through headphones, our advice is for monitors to occasionally probe the volunteer's psychological well being (e.g. ask the volunteer, 'Would you like to describe where you find yourself?') to ensure that the volunteer is not experiencing significant anxiety and is in need of support.

For studies that investigate potential therapeutic effects or the phenomenology of hallucinogen experiences (i.e. studies that do not require participants to engage in research tasks during the session), the employment of eyeshades and headphones (through which supportive music is played) may contribute to safety by reducing the distractions of environmental stimuli and social pressures to verbally interact with research personnel. This may be especially important for volunteers who are experiencing the effects of a hallucinogen for the first time. Typically, we have kept eyeshades and headphones in place for most of the session. In the latter hours of the session some time is spent with the volunteer sitting on the couch, interacting without eyeshades and headphones, although music may still be played through speakers to provide nonverbal structure and continuity. As a whole, we encourage our participants to 'collect experiences' to discuss after the drug effects have abated, and discourage attempts to analyse material or communicate excessively while the atypical states of consciousness are still occurring.

After the effects of the hallucinogen have resolved, the participant should either be released into the care of a friend or family member or required to stay overnight at the research site for monitoring. If participants are released from the study site after the session, they should be instructed not to drive an automobile or engage in any other potentially dangerous activity for the remainder of the day. At Johns Hopkins, volunteers are released into the care of a friend or family

member, who has been appropriately oriented by our staff to be available to emotionally support the participant, but also to provide space (i.e. be in another room) if the participant feels the need to be alone. We have also given the participant the primary monitor's pager number to call if he or she feels the need for support that evening. Of the 54 volunteers tested at a high psilocybin dose to date, no one has paged the monitor, although volunteers do seem to appreciate this opportunity for additional support.

Post-session procedures

After the session, safety monitoring should continue in the form of one or more post session meetings (typically the next day) between the primary monitor and participant to ensure psychological stability and provide an opportunity for the volunteer to discuss thoughts or feelings from the session. As with any acute, intense positive or negative emotional experience, participants often feel the need for, and seem to benefit from, additional time for reflecting on the novel thoughts and feelings that may have arisen in the session. Given the potentially intense and unusual psychological nature of hallucinogen effects, the volunteer may have difficulty discussing the experience with others in her or his life. Because the monitors were present during the session when the hallucinogen effects were experienced and have knowledge of a broad range of reported phenomena during drug action, the volunteer may feel more comfortable discussing her or his experience with the monitors than with others. This follow up contact also allows the assessment of any potentially persisting adverse effects, including perceptual abnormalities. More than one post session meeting may be necessary if the volunteer is experiencing psychological difficulty concerning thoughts and feelings encountered during the session. Of the 54 volunteers tested with a high dose of psilocybin at Johns Hopkins to date, none has shown evidence of persisting psychosis or psychological problems related to their sessions, and all have returned to their normal daily activities. If the primary session monitor is not a clinically trained psychologist or psychiatrist, it is prudent for research teams to have available for consultation a clinically trained psychologist or psychiatrist familiar with altered states of consciousness, who can work with patients who appear to have developed psychological difficulties stemming from hallucinogen administration.

Concluding remarks

After a decades long period of dormancy in response to the sensationalism surrounding the nonmedical use of hallucinogens during the 1960s, human hallucinogen research has resumed in the USA and Europe, and is now beginning to address a variety of important basic research questions as well as potential therapeutic applications (Nichols, 2004). In light of the unusual history of restriction on human research with this class of compounds, it is critical for investigators to implement appropriate and conservative safeguards. With such safeguards this class of compounds can be studied safely in humans. Careless research that lacks attention to the unique risk profile of hallucinogens may not only endanger the safety and well being of the research participants, but may also jeopardize future human research with these scientifically fascinating compounds. On the other hand, carefully conducted research that respects hallucinogens' unique and often powerful psychological effects may potentially inform the treatment of various psychiatric disorders, as well as lead to significant advances in our understanding of perception, cognition, behaviour, the psychology of religion and the biological underpinnings of consciousness.

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ORIGINAL ARTICL

ONLINE FIRST

Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer

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Context: Researchers conducted extensive investigations of hallucinogens in the 1950s and 1960s. By the early 1970s, however, political and cultural pressures forced the cessation of all projects. This investigation reexamines a potentially promising clinical application of hallucinogens in the treatment of anxiety reactive to advanced-stage cancer.

Objective: To explore the safety and efficacy of psilocybin in patients with advanced-stage cancer and reactive anxiety.

Design: A double-blind, placebo-controlled study of patients with advanced-stage cancer and anxiety, with subjects acting as their own control, using a moderate dose (0.2 mg/kg) of psilocybin.

Setting: A clinical research unit within a large public sector academic medical center.

Participants: Twelve adults with advanced-stage cancer and anxiety.

Main Outcome Measures: In addition to monitoring safety and subjective experience before and during experimental treatment sessions, follow-up data including results from the Beck Depression Inventory, Profile of Mood States, and State-Trait Anxiety Inventory were collected unblinded for 6 months after treatment.

Results: Safe physiological and psychological responses were documented during treatment sessions. There were no clinically significant adverse events with psilocybin. The State-Trait Anxiety Inventory trait anxiety subscale demonstrated a significant reduction in anxiety at 1 and 3 months after treatment. The Beck Depression Inventory revealed an improvement of mood that reached significance at 6 months; the Profile of Mood States identified mood improvement after treatment with psilocybin that approached but did not reach significance.

Conclusions: This study established the feasibility and safety of administering moderate doses of psilocybin to patients with advanced-stage cancer and anxiety. Some of the data revealed a positive trend toward improved mood and anxiety. These results support the need for more research in this long-neglected field.

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IN RECENT YEARS, THERE HAS BEEN a growing awareness that the psychological, spiritual, and existential crises often encountered by patients with cancer and their families need to be addressed more vigorously.[1-4] From the late 1950s to the early 1970s, research was carried out exploring the use of hallucinogens to treat the existential anxiety, despair, and isolation often associated with advanced-stage cancer.[5-15] Those studies described critically ill individuals undergoing psychospiritual epiphanies, often with powerful and sustained improvement in mood and anxiety as well as diminished need for narcotic pain medication. Despite these promising results, there has been no follow-up research.

Today, the medical value of hallucinogens is again being examined in formal psychiatric settings. One substance under investigation is psilocybin, 4-phosphoryloxy-*N*,*N*-dimethyltryptamine, which occurs in nature in various species of mushrooms. Psilocybin is rapidly metabolized to psilocin, which is a potent agonist at serotonin 5-$HT_{1A/2A/2C}$ receptors, with 5-HT_{2A} receptor activation directly correlated with human hallucinogenic activity.[16] Psilocybin was studied during the 1960s to establish its psychopharmacological profile; it was found to be active orally at around 10 mg, with stronger effects at higher doses, and to have a 4- to 6-hour duration of experience. Psychological effects were similar to those of ly-

sergic acid diethylamide (LSD), with psilocybin considered to be more strongly visual, less emotionally intense, more euphoric, and with fewer panic reactions and less chance of paranoia than LSD.[17,18]

Recent clinical examinations of psilocybin have indicated that it is not hazardous to physical health.[19] Positron emission tomographic studies demonstrated that psilocybin produces a global increase in cerebral metabolic rate of glucose, most markedly in the frontomedial and frontolateral cortex, anterior cingulate, and temporomedial cortex. These changes were correlated with measures of psychological state and consistent with potential neurobiological substrates of major mental illnesses.[20]

In one recent study, 36 healthy volunteers received a high dose (30 mg/70 kg) of psilocybin with no sustained deleterious physiological or psychological effects. The investigators corroborated previous findings that psilocybin could reliably catalyze mystical experiences leading to significant and lasting improvements in quality of life.[21] In another study, the effects of psilocybin were examined in patients with severe, refractory obsessive-compulsive disorder. Researchers concluded that psilocybin is safe and well tolerated in subjects with obsessive-compulsive disorder and may be associated with "robust acute reductions" in core obsessive-compulsive disorder symptoms, although there was no clear dose-response relationship.[22]

During the first wave of hallucinogen research from the 1950s through the early 1970s, investigators who administered hallucinogens to patients with end-stage cancers reported results that included improved mood and reduced anxiety, even in those with profound psychological demoralization.[23-26] The present study is the first in more than 35 years to explore the potential utility of a psilocybin treatment model for patients with reactive anxiety associated with advanced-stage cancer.[27]

METHODS

Twelve subjects with advanced-stage cancer and a *DSM-IV*[28] diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety were recruited into a within-subject, double-blind, placebo-controlled study to examine the safety and efficacy of psilocybin in the treatment of psychological distress associated with the existential crisis of terminal disease. Participants were recruited through Internet postings, flyer distribution, presentations at local hospitals and wellness centers, oncologist referrals, and study registration on clinicaltrials.gov and by contacting local patient support agencies and health care providers. Medical and psychiatric screening including brain magnetic resonance imaging, communication with treating oncologists, formal psychiatric diagnostic interviews, and informed consent were required for enrollment into the study. Subjects were not paid for their participation. The institutional review board of the Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, California, approved the protocol and monitored the study.

Of the 12 subjects, 11 were women. Subjects' ages ranged from 36 to 58 years. Primary cancers included breast cancer in 4 subjects, colon cancer in 3, ovarian cancer in 2, peritoneal cancer in 1, salivary gland cancer in 1, and multiple myeloma in 1. All subjects were in advanced stages of their illness. The duration of their primary cancers ranged from 2 months to 18 years. Eight subjects completed the 6-month follow-up assessment, 11 completed at least the first 4 months of assessment, and all 12 completed at least the first 3 months of follow-up. Two subjects died of their cancer during the follow-up period, and 2 others became too ill to continue participating. The study was conducted from June 2004 to May 2008. By the time of submission of this report in 2010, 10 of the 12 subjects had died.

Exclusion criteria included central nervous system involvement of the cancer, severe cardiovascular illness, untreated hypertension, abnormal hepatic or renal function, diabetes, lifetime history of schizophrenia, bipolar disease, other psychotic illness, and anxiety or affective disorders within 1 year prior to the onset of cancer. Medication contraindications included active cancer chemotherapy, antiseizure medications, insulin and oral hypoglycemics, and psychotropic medications in the previous 2 weeks. Subjects also were asked to refrain from taking any medications the day of and the day after the experimental treatment sessions, except for prescription or over-the-counter nonnarcotic pain medications at any time and narcotic pain medications up to 8 hours before and 6 hours after administration of the experimental medicine.

Four subjects had no prior hallucinogen experience. Of the remaining 8, 4 had hallucinogen experience more than 30 years ago. Two had their last experience more than 5 years ago, and the other 2 had taken a hallucinogen within the year prior to their participation in the study. Hallucinogens taken included LSD (7 subjects), hallucinogenic mushrooms (5 subjects), peyote (2 subjects), and ayahuasca (2 subjects).

Subjects met with study staff to review the purpose and intention of participation in the study, the treatment goals, the structure of the experimental treatment sessions, and critical issues to be examined during the course of the treatments. Subjects were informed of the range of emotional reaction that might be experienced while under the influence of psilocybin, including challenging psychological issues that might arise, and were informed that the purpose of the investigation was to determine whether psilocybin could ameliorate the anxiety associated with their advanced-stage cancer. Additional goals of these meetings included establishing a comfortable level of rapport and trust between the patient and research personnel, reviewing significant life issues in the patient's history, and the nature and status of present relationships and concerns.

All experimental sessions took place in a hospital clinical research unit in a room decorated with fabric wall hangings and fresh flowers to provide a pleasing and comfortable environment. Subjects were admitted on the afternoon of the day prior to treatment. A Holter cardiac monitor was attached for 24 hours beginning at admission. Following medical and nursing evaluations, the treatment team met with the subject to review the procedure for the treatment session (described later), confirm the subject's personal intentions, and answer any additional questions. Subjects spent the night in the room on the research unit and were provided dinner and a light breakfast before 06:30 hours. On the morning of treatment, the therapeutic team met with the subject to administer presession instruments, attend to patient comfort, and review treatment procedures for the session one final time.

Each subject acted as his or her own control and was provided 2 experimental treatment sessions spaced several weeks apart. They were informed that they would receive active psilocybin (0.2 mg/kg) on one occasion and the placebo, niacin (250 mg), on the other occasion. Psilocybin and placebo were administered in clear 00 capsules with corn starch and swallowed with 100 mL of water. A niacin placebo was chosen because it often induces a mild physiological reaction (eg, flush-

ing) without altering the psychological state. The order in which subjects received the 2 different treatments was randomized and known only by the research pharmacist. Treatment team personnel remained at the bedside with the subject for the entire 6-hour session.

Psilocybin or placebo was administered at 10:00 hours. The subject was encouraged to lie in bed wearing eye shades during the first few hours as well as to put on headphones to listen to preselected music. Subjects were allowed to remain undisturbed until each hour point, when treatment staff checked to inquire how they were doing. Contact was generally brief; subjects had been advised that there would be ample opportunity after the session and in subsequent days, weeks, and months to discuss the content of the experience. During hourly check-ins, heart rate (HR) and blood pressure (BP) measurements also were taken. Noncaffeinated clear liquids or juices were permitted.

At the conclusion of the 6-hour session, subjects discussed the subjective aesthetic, cognitive, affective, and psychospiritual experiences they had during the session and completed rating instruments. Various self-report inventories and questionnaires were administered from 2 weeks prior to the first treatment session to up to 6 months after the second. Treatment team personnel maintained contact with subjects for the entire 6-month follow-up period, including regularly scheduled monthly telephone calls to update data on adverse events, concomitant medications, and evolving medical and psychological status.

ASSESSMENT MEASURES

Subjects' BP and HR were measured 30 minutes before drug ingestion, immediately before drug administration, and at hourly intervals for the next 6 hours. Temperature was measured just prior to drug administration and 6 hours later at the conclusion of the session.

The following psychological measures were administered the day before each of the experimental sessions: the Beck Depression Inventory (BDI), Profile of Mood States (POMS), and State-Trait Anxiety Inventory (STAI). The POMS, STAI, 5-Dimension Altered States of Consciousness profile (5D-ASC), and Brief Psychiatric Rating Scale were administered at the conclusion of the experimental sessions. The day after the session, the BDI, POMS, and STAI were readministered. Finally, the BDI, POMS, and STAI were administered again 2 weeks after each session and at monthly intervals for 6 months after the final session.

INSTRUMENTS

Beck Depression Inventory

The BDI consists of a series of questions developed to measure the intensity, severity, and depth of depression.[29]

Profile of Mood States

The POMS describes feelings individuals have, with the subject indicating his or her mood during the past week, including the present day. The POMS Brief, used for this study, is a shorter version of the original POMS Standard.[30] Subjects were instructed to fill out the POMS and BDI in reference to their feelings during the past week.

State-Trait Anxiety Inventory

The STAI Form Y is a widely used self-report instrument for assessing anxiety in adults. It includes separate measures of state and trait anxiety.[31] The STAI evaluates the essential qualities of feelings of apprehension, tension, nervousness, and worry. The STAI differentiates between the temporary condition of state anxiety and the more general and long-standing quality of trait anxiety. The STAI state anxiety subscale asks for feelings at the moment of filling out the questionnaire, and the STAI trait anxiety subscale asks subjects to indicate how they generally view themselves.

Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale provides clinician assessment of the level of symptoms such as hostility, suspiciousness, hallucination, and grandiosity.[32]

5-Dimension Altered States of Consciousness Profile

The 5D-ASC rating scale measures alterations in mood, perception, experience of self in relation to environment, and thought disorder.[33] The ASC items are grouped into 5 subscales comprising several items, including the following: (1) *oceanic boundlessness*, measuring derealization and depersonalization accompanied by changes in affect ranging from elevated mood to euphoria; (2) *anxious ego dissolution*, measuring ego disintegration associated with loss of self-control, thought disorder, arousal, and anxiety; (3) *visionary restructuralization*, including hallucinations, pseudohallucinations, synesthesia, changed meaning of perceptions, and facilitated recollection and imagination; (4) *auditory alterations*, with acoustic alterations and alterations of auditory experiences; and (5) *reduction of vigilance*, associated with drowsiness, reduced alertness, and related impairment of cognition. Subjects filled out the 5D-ASC at the conclusion of the session.

DATA ANALYSIS

Raw BDI, POMS, and STAI data were analyzed using 2-way analysis of variance (ANOVA) with drug as the within-subject factor and day as a repeated measure. When the 2-way ANOVA detected significant main effects of drug or interactions between day and drug, post hoc pairwise comparisons were performed by 1-way ANOVA for each day. The 5D-ASC data were analyzed using 1-way ANOVA with drug as a within-subject factor. Item clusters comprising the oceanic boundlessness, anxious ego dissolution, and visionary restructuralization dimensions also were analyzed using 1-way ANOVA.[34] The Brief Psychiatric Rating Scale data were analyzed using 1-way ANOVA with drug as a within-subject factor. The HR and BP data were analyzed using 2-way ANOVA with drug as a within-subject factor and time as a repeated measure. When the 2-way ANOVA detected significant main effects of drug or interactions between time and drug, pairwise post hoc comparisons were performed by 1-way ANOVA at each time. For the measures listed earlier, significance was demonstrated by surpassing an α level of .05. Paired *t* tests were used to assess whether niacin placebo and psilocybin produced effects on HR and BP compared with the predrug time, and significance was demonstrated for these multiple comparisons by surpassing an α level of .025. For the BDI, POMS, and STAI, data from each of the 6 follow-up times were compared with the baseline value obtained on the day before the first treatment session, using *t* tests. For the follow-up data, significance was demonstrated by surpassing an α level of .05.

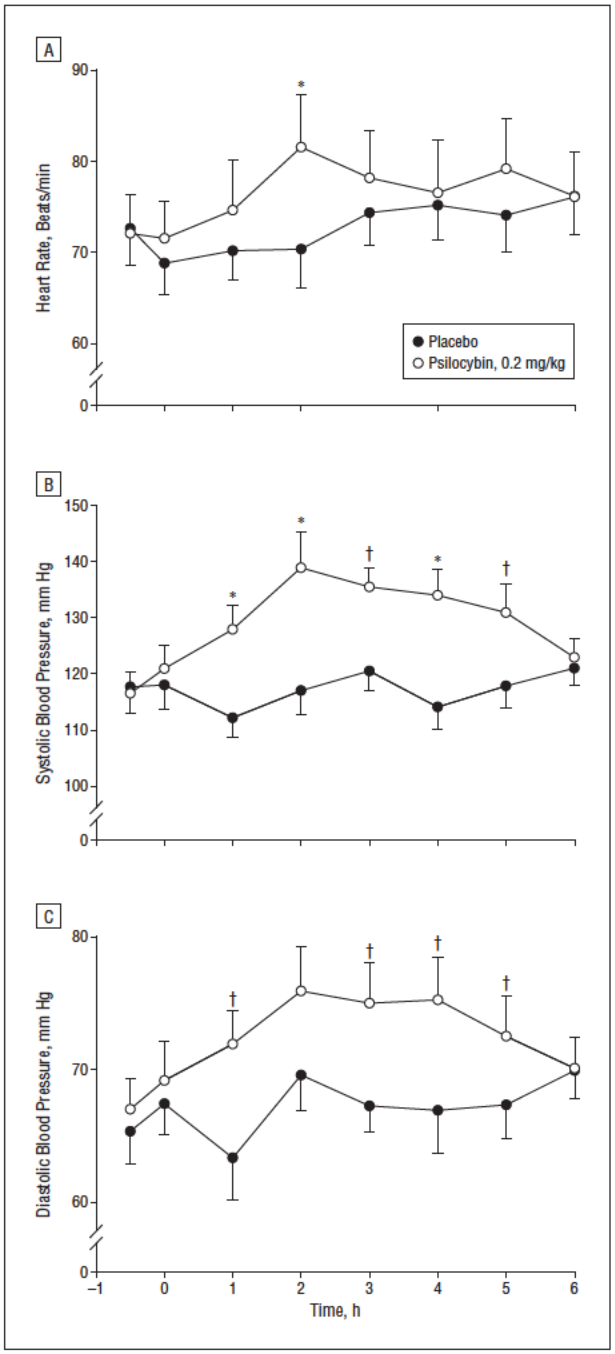

Figure 1. Effect of psilocybin or niacin placebo on mean (SEM) heart rate (A), systolic blood pressure (B), and diastolic blood pressure (C). Psilocybin or niacin placebo was administered at 0 hours.*$P<.01$, †$P<.05$ for psilocybin vs niacin placebo control (1-way analyses of variance were used to compare niacin and psilocybin effects at individual times).

RESULTS

CARDIOVASCULAR FUNCTION

The administration of psilocybin at a dose of 0.2 mg/kg induced a mild but statistically significant elevation of HR (psilocybin × time interaction: $F_{7,70}=2.40$, $P=.03$), systolic BP ($F_{1,11}=25.39$, $P<.001$), and diastolic BP ($F_{1,11}=5.94$, $P=.03$) when compared with niacin placebo. Elevation of HR peaked 2 hours after psilocybin administration, with a mean (SEM) peak effect of 81.5 (5.8) beats/min, which was statistically significant ($F_{1,11}=11.31$, $P<.007$) compared with 70.4 (4.3) beats/min during placebo sessions (**Figure 1**A).

Blood pressure also peaked at the 2-hour point, with mean (SEM) peak systolic BP during psilocybin sessions measuring 138.9 (6.4) mm Hg (compared with 117.0 [4.3] mm Hg during niacin placebo sessions) (Figure 1B) and mean (SEM) peak diastolic BP of 75.9 (3.4) mm Hg during psilocybin sessions (compared with 69.6 [2.7] mm Hg during niacin placebo sessions) (Figure 1C). Holter monitor recordings during the psilocybin sessions showed no sustained tachyarrhythmias or heart block and were consistent with findings during active placebo sessions. Compared with the predrug time, niacin modestly depressed diastolic BP 1 hour after administration (Figure 1C) with a rebound over the next hour but had no effect at other times.

PSYCHOLOGICAL MEASURES

The 5D-ASC demonstrated marked subjective differences between the psilocybin and placebo experiences. Psilocybin particularly affected the oceanic boundlessness ($F_{1,11}=33.12$, $P<.001$) and visionary restructuralization ($F_{1,11}=18.95$, $P=.001$) dimensions (**Figure 2**A). Psilocybin had smaller but significant effects on anxious ego dissolution ($F_{1,11}=4.91$, $P=.049$) and auditory alterations ($F_{1,11}=5.93$, $P=.03$). The item clusters with marked differences between the subjective states produced by psilocybin and niacin included a significant increase ($P<.05$) in psilocybin-invoked states of positive derealization, positive depersonalization, altered sense of time, positive mood, manialike experiences, elementary hallucinations, visual pseudohallucinations, synesthesia, changed meaning of percepts, facilitated recollection, and facilitated imagination. Subscales with no appreciable differences between intrasubjective states induced by the 2 treatments included anxious derealization, thought disorder, delusion, fear of loss of thought control, and fear of loss of body control (Figure 2B).

For the BDI, there was an overall interaction of psilocybin and day that approached but did not attain statistical significance ($F_{1,11}=3.75$, $P=.08$). There was no appreciable change from 1 day prior to placebo administration to 2 weeks after experimental treatment, whereas a trend was observed after psilocybin administration, from a mean (SEM) score of 16.1 (3.6) one day before treatment to 10.0 (2.7) two weeks after treatment (**Figure 3**A). As shown in Figure 3B, BDI scores dropped by almost 30% from the first session to 1 month after the second treatment session ($t_{11}=-2.17$, $P=.05$), a difference that was sustained and became significant at the 6-month follow-up point ($t_7=2.71$, $P=.03$).

The POMS similarly revealed a trend for reduced adverse mood tone from 1 day before treatment with psilocybin to 2 weeks later, a difference that was not seen after placebo (drug × time interaction: $F_{3,33}=2.71$, $P=.06$) (**Figure 4**A). Paired post hoc tests revealed that mean (SEM) POMS scores were elevated ($F_{1,11}=7.48$, $P=.02$) 1 day before psilocybin treatment (11.3 [3.1]) compared with 1 day before placebo (4.5 [2.0]) and demonstrated

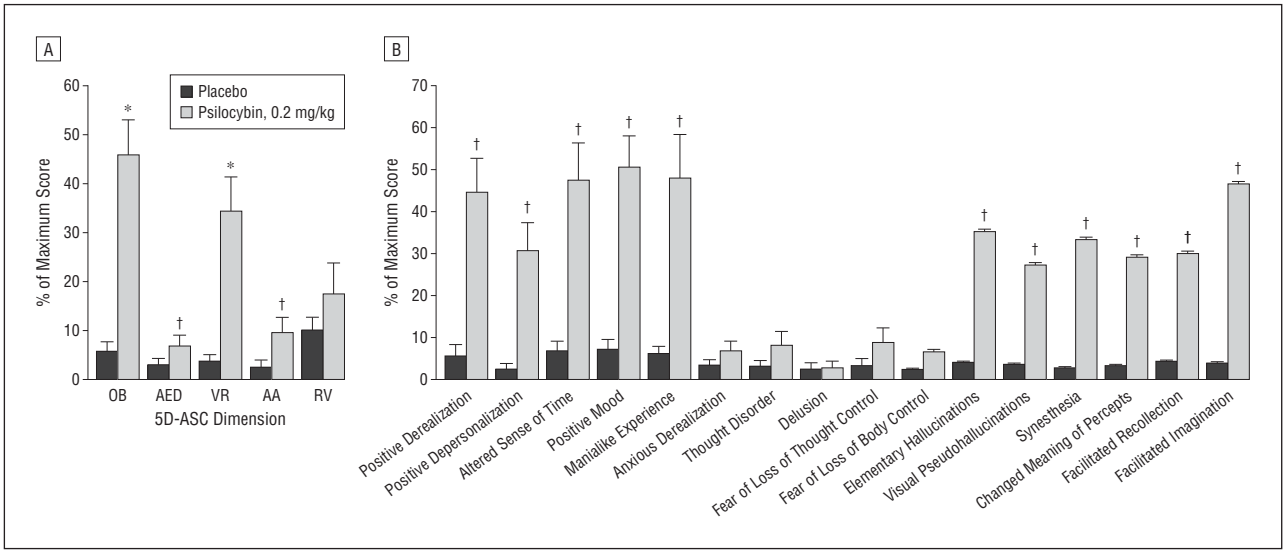

Figure 2. Subjective effects of psilocybin as measured by the 5-Dimension Altered States of Consciousness profile (5D-ASC). A, Five main 5D-ASC dimensions are shown: oceanic boundlessness (OB), anxious ego dissolution (AED), visionary restructuralization (VR), auditory alterations (AA), and reduced vigilance (RV). B, Item clusters comprising the OB, AED, and VR dimensions are shown. Values are the mean (SEM) percentages of the total possible score. *$P<.01$, †$P<.05$ for psilocybin vs niacin placebo control (1-way analyses of variance were used to compare niacin and psilocybin effects on individual 5D-ASC dimensions and 5D-ASC item clusters).

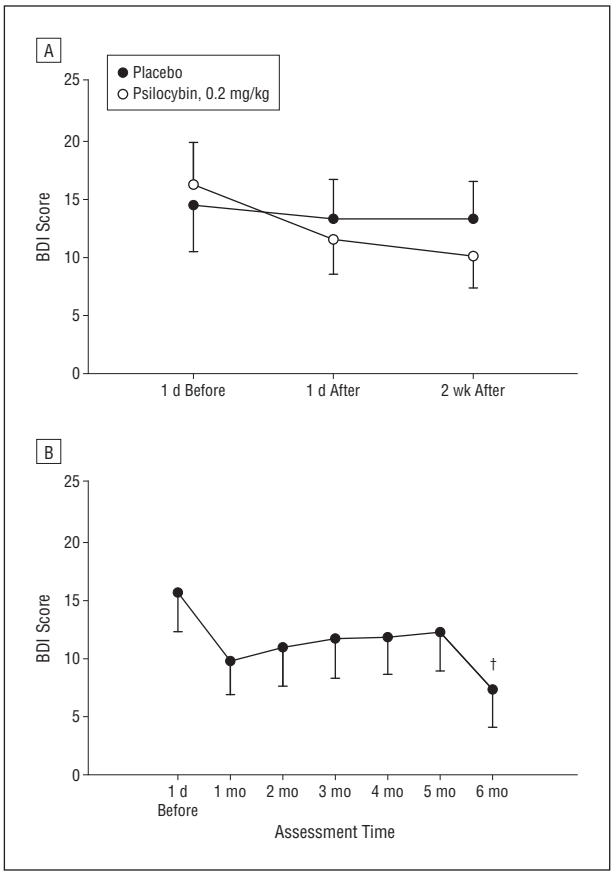

Figure 3. Beck Depression Inventory (BDI) scores. A, Mean (SEM) BDI scores 1 day before, 1 day after, and 2 weeks after administration of psilocybin or niacin placebo are shown. B, Six months of mean (SEM) BDI follow-up data are shown. The BDI was administered at monthly intervals for 6 months after the second treatment session, and the 6 sets of monthly follow-up data were compared with the scores obtained the first time the participants filled out the instruments (ie, 1 day before the first treatment session). †$P<.05$ for psilocybin vs the value from 1 day before the first treatment session (t tests were used to compare individual monthly follow-up values with values on the day before the first session).

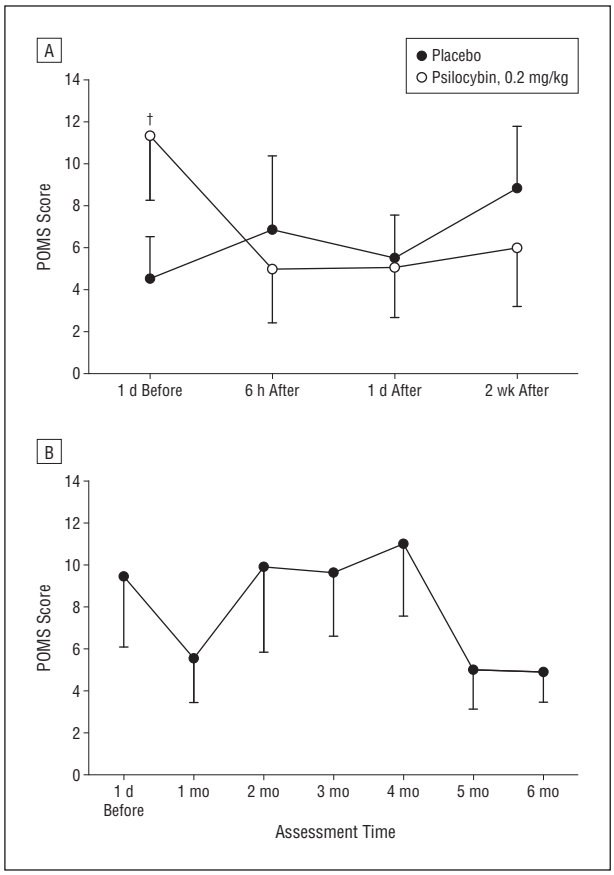

Figure 4. Profile of Mood States (POMS) scores. A, Mean (SEM) POMS scores 1 day before, 6 hours after, 1 day after, and 2 weeks after administration of psilocybin or niacin placebo are shown. B, Six months of mean (SEM) POMS follow-up data are shown. The POMS was administered at monthly intervals for 6 months after the second treatment session, and the 6 sets of monthly follow-up data were compared with the scores obtained the first time the participants filled out the instruments (ie, 1 day before the first treatment session). †$P<.05$ for psilocybin vs niacin placebo control (1-way analyses of variance were used to compare niacin and placebo effects at individual times).

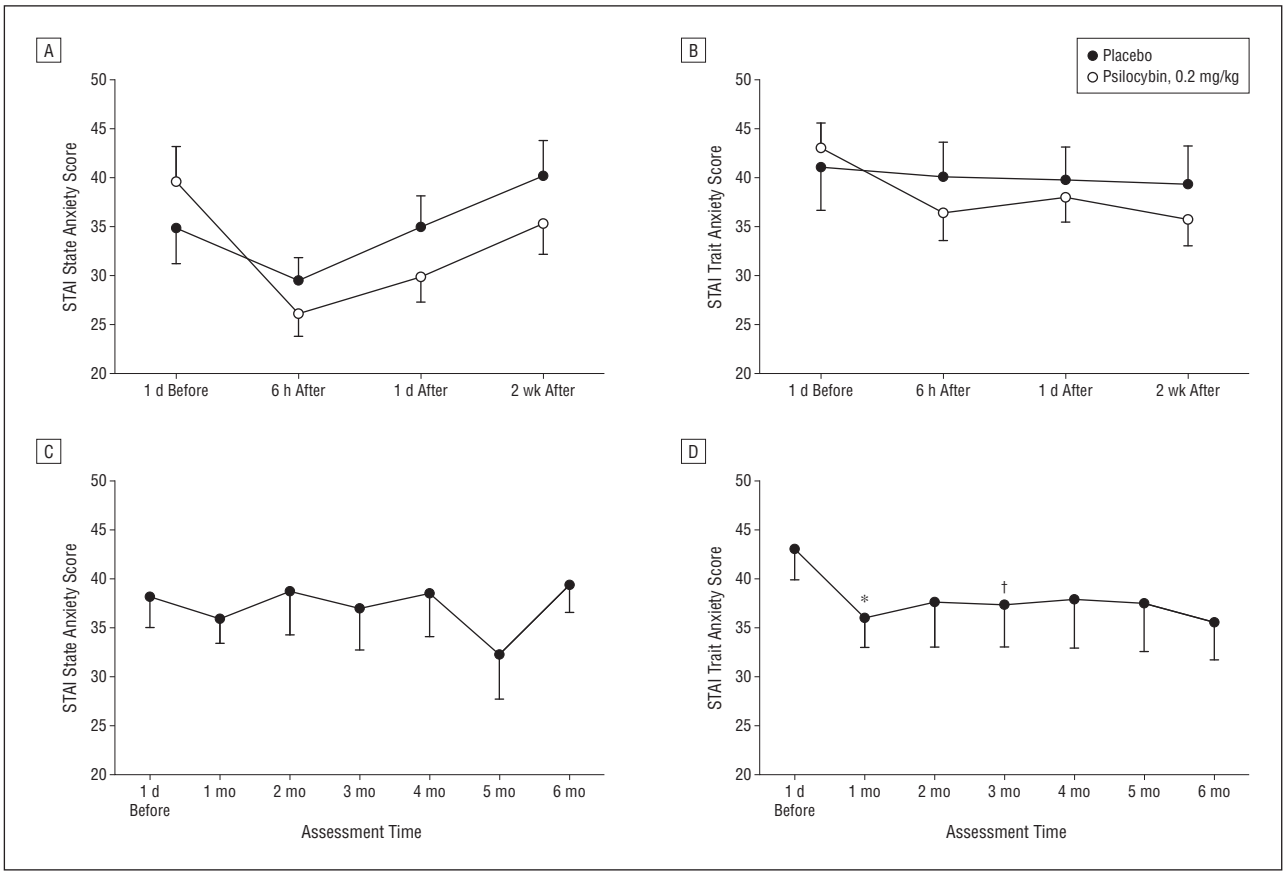

Figure 5. Mean (SEM) State-Trait Anxiety Index (STAI) state anxiety scores (A) and trait anxiety scores (B) 1 day before, 6 hours after, 1 day after, and 2 weeks after administration of psilocybin or niacin placebo are shown. Six months of mean (SEM) STAI state anxiety follow-up data (C) and trait anxiety follow-up data (D) are shown. The STAI was administered at monthly intervals for 6 months after the second treatment session, and the 6 sets of monthly follow-up data were compared with the scores obtained the first time the participants filled out the instruments (ie, 1 day before the first treatment session). *$P<.01$, †$P<.05$ for psilocybin vs the value from 1 day before the first treatment session (t tests were used to compare individual monthly follow-up values with values on the day before the first session).

that this difference disappeared 6 hours after psilocybin administration. Improvement of mood, indicated by reduced POMS scores, was observed in 11 subjects after administration of psilocybin. The elevation of POMS scores 1 day before psilocybin treatment occurred regardless of whether the subjects were treated with placebo or psilocybin first (ie, there was no interaction between treatment order and drug). As shown in Figure 4B, POMS scores were not altered during the 6 months of follow-up compared with the day before the first treatment session.

The STAI revealed no significant changes from 1 day before to 2 weeks after treatment, although a substantial but nonsignificant decrease was evident for the state anxiety subscale 6 hours after psilocybin administration, which was not observed after placebo (**Figure 5**A and C). Although minimal change was observed in the STAI state anxiety score for follow-up data, a sustained decrease in STAI trait anxiety was observed for the entire 6-month follow-up, reaching significance at the 1-month ($t_{11}=4.36$, $P=.001$) and 3-month ($t_{10}=2.55$, $P=.03$) points after the second treatment session (Figure 5B and D).

The Brief Psychiatric Rating Scale at the end of the experimental session revealed no appreciable difference between psilocybin and placebo administration.

COMMENT

The initial goals of this research project were to establish feasibility and safety for a hallucinogen treatment model in patients with advanced-stage cancer and anxiety. Following discussion with federal and state regulatory agencies as well as hospital institutional review board and research committees, a modest 0.2-mg/kg psilocybin dose was chosen. Although not comparable to higher doses of hallucinogens administered in the past to severely ill patients, the dose used here was still believed capable of inducing an alteration of consciousness with potential therapeutic benefit while optimizing patient safety. Determining safe parameters with this novel treatment paradigm is critical to establishing a strong foundation for this field of study that would allow for future investigations.

Consistent with previous research, we found no untoward cardiovascular sequelae in our subject population.[19] Minor HR and BP elevations after psilocybin administration were evidence only of a mild sympathomimetic effect. Holter monitoring did not identify increased cardiac arrhythmias in comparison with niacin placebo, even in subjects who presented with some baseline cardiac arrhythmia. Niacin may acutely lower BP through vasodi-

lation[35] but had minimal effects on BP and HR in our subjects, except for a reduction in diastolic BP that was noted 1 hour after administration of niacin. This transient effect may have contributed to our detection of a significant psilocybin effect at that time but cannot explain the significant effects of psilocybin over the subsequent intervals because the initial niacin-induced reduction of diastolic BP did not persist. We also observed no adverse psychological effects from the treatment. All subjects tolerated the treatment sessions well, with no indication of severe anxiety or a "bad trip." The fact that psilocybin produced only modest effects on the anxious ego dissolution scale of the 5D-ASC confirmed this conclusion.

When hallucinogens were administered to patients with terminal cancer in the 1960s and early 1970s, the occurrence of a profound psychospiritual experience was correlated with therapeutic outcome.[10,12] Such transcendent states of consciousness are usually associated with higher doses of hallucinogens, so our expectation of demonstrating efficacy was limited.[21] Common themes reported by subjects included examining how their illness had impacted their lives, relationships with family and close friends, and sense of ontological security. In addition, subjects reported powerful empathic cathexis to close friends and family members and examined how they wished to address their limited life expectancy. In monthly follow-up discussions, subjects reflected on insights and new perspectives gained during their psilocybin treatment. However, the frequency of these reports was not quantified.

Although past researchers reported more pronounced therapeutic effects with a higher-dose model, even the lower dose of psilocybin used in the current study gave some indication of therapeutic benefit in quantitative psychological evaluations. In particular, we found that the STAI trait anxiety subscale demonstrated a sustained reduction in anxiety that reached significance at the 1- and 3-month points after treatment. This reduction might reflect a reduced level of stress and anxiety over time. Although the state anxiety on the STAI showed a modest elevation at 6 months, the change was not statistically significant and might have resulted from the deteriorating medical status of most subjects over time.

Mood also improved for 2 weeks after treatment with psilocybin, with sustained improvement on the BDI reaching significance at the 6-month follow-up point. The POMS scores also reflected improved mood 2 weeks after receiving psilocybin. Although not statistically significant, there was a trend toward positive outcome. With a larger cohort of subjects and use of a higher dose of psilocybin, it seems possible that significant results would be obtained on these measures.

Compared with placebo sessions, POMS scores were elevated in subjects immediately prior to psilocybin administration. The reasons for this difference in POMS scores 1 day before administration are not entirely clear. Subject expectations were unlikely to have played a role in the elevation of the POMS scores on the day before treatment because the elevation occurred regardless of treatment order. The most likely explanation for the elevation of POMS scores prior to treatment with psilocybin may be that subject randomization was not complete with regard to this instrument. Nonetheless, POMS scores declined after administration of psilocybin in 11 of 12 subjects, suggesting that psilocybin produces mood-elevating effects that persist after the acute effects of the drug.

Another focus of the study was the effect of a 0.2-mg/kg psilocybin dose on somatic symptoms, particularly pain perception. In contrast to previous investigations, we did not find robust reductions in pain perception or lessened need for narcotic pain medication. In the 2 weeks following experimental treatment sessions, several subjects reported lessened pain, whereas others did not. There was no apparent difference between subjects treated with psilocybin and those treated with placebo (data not shown). Although this modest dose of psilocybin was not observed to impact pain, given the impressive reports of earlier researchers,[6] this measure would certainly be indicated for study with higher doses.

Although we used a within-subject, double-blind, placebo-controlled design, the drug order was almost always apparent to subjects and investigators whether the treatment was psilocybin or placebo. In fact, one consistent subject critique of the study was that the placebo sessions were perceived as far less worthwhile than those with psilocybin. Many of the subjects suggested that future protocols provide the opportunity for a second psilocybin session several weeks after the first. The general consensus among subjects was that a follow-up experience with psilocybin would reinforce and extend the perceived therapeutic effects of the initial session.

Future studies also will need to address the issue of controlling for a placebo effect that might otherwise be attributed to the active treatment. Given the subjects' grave prognosis and limited life expectancy, we decided to provide all subjects with an opportunity to experience the experimental medicine and to serve as their own control. Although we believed that to be the ethical course to take, given the life circumstances subjects were encountering, the protocol design contains some inherent limitations. A better experimental design might incorporate an independent control group, receiving only either placebo treatment or a conventional psychopharmacological intervention. Although there is no question that the extensive attention paid to the subjects influenced outcomes, the unique qualities of the psilocybin experience in facilitating strong therapeutic bonds and ameliorating underlying psychological demoralization are important factors worthy of further exploration.

Another limitation of this study was variability in the extent of contact with subjects after treatment. A minimum contact of 1 hour monthly was established, but variability in additional ad hoc communication depended on the needs and wishes of the subjects, some of whom were near death compared with others who were more functional.

Despite the limitations, this study demonstrates that the careful and controlled use of psilocybin may provide an alternative model for the treatment of conditions that are often minimally responsive to conventional therapies, including the profound existential anxiety and despair that often accompany advanced-stage cancers. A recent review from the psilocybin research group at Johns Hopkins University describes the critical components necessary for ensuring subject safety in hallucinogen research.[36]

Taking into account these essential provisions for optimizing safety as well as adhering to strict ethical standards of conduct for treatment facilitators, the results provided herein indicate the safety and promise of continued investigations into the range of medical effects of hallucinogenic compounds such as psilocybin.

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The Abuse Potential of Medical Psilocybin According to the 8 Factors of the Controlled Substances Act

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Abstract

This review assesses the abuse potential of medically-administered psilocybin, following the structure of the 8 factors of the US Controlled Substances Act (CSA). Research suggests the potential safety and efficacy of psilocybin in treating cancer-related psychiatric distress and substance use disorders, setting the occasion for this review. A more extensive assessment of abuse potential according to an 8 factor analysis would eventually be required to guide appropriate schedule placement.

Psilocybin, like other 5-HT2A agonist classic psychedelics, has limited reinforcing effects, supporting marginal, transient non-human self-administration. Nonetheless, mushrooms with variable psilocybin content are used illicitly, with a few lifetime use occasions being normative among users. Potential harms include dangerous behavior in unprepared, unsupervised users, and exacerbation of mental illness in those with or predisposed to psychotic disorders. However, scope of use and associated harms are low compared to prototypical abused drugs, and the medical

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Declaration of conflicting interests
The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Roland Griffiths is on the Board of Directors of the Heffter Research Institute which supports psilocybin research and the potential development and submission of an NDA to the United States Food and Drug Administration (US FDA).
Through, Pinney Associates, Jack Henningfield has consulted and/or are presently consulting to the Heffter Research Institute and to the Usona Institute which are supporting the development of psilocybin as a new medication to be submitted for approval by the U.S. FDA, as well as to other sponsors of central nervous system acting products concerning their abuse potential, appropriate regulation, and medicinal application.

model addresses these concerns with dose control, patient screening, preparation and follow-up, and session supervision in a medical facility.

Conclusions: (1) psilocybin has an abuse potential appropriate for CSA scheduling if approved as medicine; (2) psilocybin can provide therapeutic benefits that may support the development of an approvable new drug application (NDA) but further studies are required which this review describes; (3) adverse effects of medical psilocybin are manageable when administered according to risk management approaches; and (4) although further study is required, this review suggests that placement in Schedule IV may be appropriate if a psilocybin-containing medicine is approved.

Keywords

psilocybin; abuse potential; Controlled Substances Act; depression; anxiety; addiction

1. Introduction

Psilocybin (4-phosphoryloxy-N,N-dimethyltryptamine) is under development for the treatment of depression and anxiety for patients with life-threatening cancer diagnoses (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016). Although at a more preliminary research state, promising open label results have also been reported for treatment-resistant major depression (Carhart-Harris et al., 2016a; Rucker et al., 2017) and addiction to tobacco (Johnson et al., 2014) and alcohol (Bogenschutz et al., 2015). Such treatments would be in the form of a clinically tested drug product that would provide psilocybin doses demonstrated to be safe and effective in a formulation that assures precision in dosing, which is rarely the case for illicitly consumed mushrooms (Bigwood and Beug, 1982), and in a clinical framework that would minimize the possibility of misuse or diversion. These drug formulation and intervention parameters would be addressed in an agreed upon risk management plan and would also likely be addressed in a legally binding Risk Evaluation and Mitigation Strategies (REMS) plan (U.S. Food and Drug Administration, 2015). The REMS would be based on the studies and approaches used to ensure safe and effective use and could include: a) limitations on the dose and the number of doses that could be administered to a given patient, b) administration of the drug in clinic settings with psychological support of specially trained staff, c) a variety of restrictions on distribution, access and storage, and d) a post-marketing surveillance plan to provide the FDA with timely and comprehensive communication of unintended consequences (Blanchette et al., 2015; Brandenburg et al., 2017; Dart, 2009; Dasgupta and Schnoll, 2009; U.S. Food and Drug Administration, 2015; Wu and Juhaeri, 2016).

The benefits of psilocybin in the treatment of depression, anxiety and other disorders were first suggested in the 1960s when psilocybin was marketed in many countries, including the United States (US) under the trade name Indocybin® by the Swiss pharmaceutical company, Sandoz. Indocybin® provided a shorter acting alternative to lysergic acid diethylamide (LSD) which has a similar primary pharmacological mechanism of action, now known to be agonist or partial agonist effects at the 5-HT2A receptor (Nichols, 2016). While Indocybin® was used safely as an adjunct to psychotherapy, eventually the societal backlash in the US and other countries in the 1960s (Matsushima et al., 2009) led to a ban on marketing and

possession of “hallucinogenic” drugs in the US in 1965, and led Sandoz to discontinue manufacturing and marketing of Indocybin® in 1966 (Belouin and Henningfield, 2018; Bonson, 2018; Novak, 1997). The 1970 placement of psilocybin, LSD, and other “hallucinogens” in Schedule I of the CSA did not reflect an absence of therapeutic benefit, although the scientific evidence at the time was mixed. This mixed evidence included strong (at least for the time) pharmacological studies as discussed later in this review, along with clinical studies suggesting potential safety and efficacy that were nonetheless considered by leading researchers during the 1960s to be limited and not sufficient to support efficacy and safety claims for LSD or other hallucinogens. This situation is discussed by Bonson (2018) in her review of human LSD research and regulation, and would appear to generally apply to psilocybin, which was being administered by some of the same research programs that administered LSD. These limitations in the evidence base and the rising tide of sensational media accounts of adverse consequences of classic psychedelic use, discussed later, fueled the perception by many public and political leaders that psilocybin posed serious risks to patients and the public that did not outweigh its benefits (Belouin and Henningfield, 2018; Hofmann, 1980; Nutt et al., 2013). Therefore, having not been formally approved by the FDA for therapeutic use, psilocybin was placed in Schedule I of the CSA in 1970 and remains in Schedule I.[1]

As discussed in section 1.1, removal from Schedule I can only occur if a medicinal product containing a Schedule I substance is approved for therapeutic use as a drug by the FDA. Then, whether it will be scheduled, and, if so, into what schedule it will be placed, will be subject to the FDA’s abuse potential assessment that will include an analysis of the 8 factors of the CSA (Drug Enforcement Administration, 2017a; U.S. Food and Drug Administration, 2017a). As discussed by Calderon, Hunt and Klein in this journal issue, schedule placement is a process that considers “potential for abuse, medical use, and physical or psychological dependence liability,” among other lines of evidence (Calderon et al., 2017). For example, approval of the Schedule I compounds dextrorphan and difenoxin (with atropine) resulted in dextrophan becoming unscheduled, and difenoxin (with atropine) being placed into either Schedule IV or V, depending on dose. Similarly, the previously Schedule I compound piperazine was descheduled. Approval of an oral form of dronabinol (marinol) was initially placed in Schedule II and, in 1999, rescheduled to Schedule III, leaving cannabis and forms of dronabinol that were not approved drug products in Schedule I. As noted by Calderon et al., approved drugs with hallucinogenic effect vary widely in the scheduling from the Schedule I status of most hallucinogenic drugs without approved medical use, to Schedule II phencyclidine, Schedule III ketamine, and Schedule IV lorcaserin, and the not scheduled 2,5-dimethoxy-4-iodoamphatamine, also known as DOI (Calderon et al., 2017).

[1]Schedule I of the CSA is reserved for substances determined by DEA to “have a high potential for abuse, no currently accepted medical use in treatment in the United States, and a lack of accepted safety for use under medical supervision.” This includes substances that were determined to warrant placement in Schedule I when the CSA was enacted into law in 1970, and substances that have not been approved by FDA for medical use but were placed in Schedule I based on DEA’s 8-factor analysis, or temporarily placed (also commonly termed “emergency scheduled”) in Schedule I if DEA determines such placement “is necessary to avoid an imminent hazard to the public safety.” For such scheduling the DEA is required to consider only factors 4, 5 and 6 of the CSA, namely, the substance’s history and current pattern of abuse; the scope, duration and significance of abuse; and what, if any, risk there is to the public health, respectively (Calderon et al., 2017; Drug Enforcement Administration, 2017a; Henningfield et al., 2017; Pinney Associates, 2016; U.S. Food and Drug Administration, 2017a).

Thus, if an NDA for a psilocybin product is submitted to the FDA and approved, then the CSA would require its rescheduling, and schedule placement would be determined by evaluation of its overall abuse potential (Drug Enforcement Administration, 2017a; Henningfield et al., 2017; U.S. Food and Drug Administration, 2017a). In fact, as discussed in Belouin and Henningfield (2018) (in this journal issue), there is increasing evidence supporting the eventual development and submission of an NDA for a psilocybin-containing product. Emerging science suggesting benefits of a psilocybin product warrant an official breakthrough designation by the FDA to address the large number of cancer sufferers whose depression and anxiety are not responsive to conventional therapies (Belouin and Henningfield, 2018; Griffiths and Johnson, 2015; Ross et al., 2016). In addition, advances in risk management and monitoring, which were absent in the earlier heyday of psychedelic research, necessitate that we revisit the potential for approving a classic psychedelic (i.e., psilocybin) as a medicine because risk management, particularly in the legally binding approach of REMS, is intended to provide conditions for distribution, use, oversite and other factors to ensure safe use (McCormick et al., 2009; U.S. Food and Drug Administration, 2015).

Clinically, chemically, and pharmacologically, psilocybin has similarities with several substances that were generally termed “hallucinogens” in the 1950s and have been termed “psychedelics” since the 1960s. Although both of these terms are sometimes used to refer to compounds with other primary mechanisms of action (e.g., ketamine; salvinorin A, methylenedioxymethamphetamine or MDMA), 5-HT2A receptor agonist compounds, including psilocybin, LSD, mescaline, and dimethyltryptamine (DMT), are specifically referred to as “classic psychedelics” or “classic hallucinogens.” Although there are similarities in the effects, patterns of use and past clinical applications of LSD, psilocybin, and other classic psychedelics, the present evaluation is focused on a drug product in which the active ingredient is psilocybin. Moreover, approval would include not only the compound, but also its labeling and restrictions on manufacturing, marketing and use. These additional domains are critical to the benefit to risk evaluations which are foundational for drug evaluation and approval (U.S. Food and Drug Administration, 2017c).

Research and licit clinical use of LSD and psilocybin greatly slowed in the 1960s as amendments in 1962 and 1965 to the 1938 US Food Drug and Cosmetic Act imposed severe restrictions on distribution, possession, use, and research (Barrigar, 1964; Bonson, 2018; Grabowski, 1976; Grinspoon and Bakalar, 1979). As discussed elsewhere in this journal issue and in other publications (Nutt, 2015; Nutt et al., 2013; Scientific American Editors, 2014; Sinha, 2001; Spillane, 2004; Woodworth, 2011), legal restrictions have greatly constrained research; however, research did not altogether cease, and began to accelerate by the late 1980s in preclinical laboratories, and in clinical settings by the late 1990s. This resurgence has been fueled in part by renewed appreciation of the potential importance of these substances in advancing the science of the brain and behavior and for their potential significance in the treatment of disease. Moreover, since the 1970s extensive national drug use and effects surveillance systems have been developed in the US, which show that the prevalence of abuse and serious adverse events associated with psilocybin and other classic psychedelics are relatively low compared to other major classes of abused drugs (Johnson, Hendricks, Barrett, Griffiths, submitted). In addition to the more recent clinical research, the

reassuring results from these epidemiological data also increase interest in the evaluation of psilocybin as a potential therapeutic medicine (Roseman et al., 2017; Rucker et al., 2017). Because the FDA approved therapeutic medicines cannot be listed in Schedule I of the CSA, consideration of changes in scheduling recommendations becomes an important part of the clinical development of psilocybin. As discussed in this review the evidence continues to support the conclusion that if a psilocybin drug product was approved by the FDA, CSA scheduling would remain appropriate. Considerable additional study will be required for the development of an FDA-acceptable NDA, including the abuse potential assessment section of the NDA according to the FDA's abuse potential assessment guidance (U.S. Food and Drug Administration, 2017a). Thus, it is premature to come to a definitive conclusion about which schedule would be most appropriate. This review is intended to stimulate further research and thinking in this area through its evaluation of key abuse potential-related science presently available and considered through the approach of the CSA 8-factor analysis which is the key approach of the CSA for developing scheduling recommendations. The review includes a preliminary scheduling conclusion based on the research considered and the opinions of these authors, along with key gaps in the research that will also likely be of importance to the FDA.

1.1 Abuse potential and drug scheduling in the context of the CSA

The scheduling process for new drugs officially commences upon approval of the product by the Controlled Substances Staff (CSS) of the FDA, who provide an 8-factor analysis based, in part, on the sponsor's submission of an NDA that includes the sponsor's abuse potential assessment that has been prepared according to the recommendations in the FDA's guidance for sponsors: Assessment of the Abuse Potential of Drugs (U.S. Food and Drug Administration, 2017a). The FDA obtains review and input from the National Institute on Drug Abuse (NIDA). Then, the Assistant Secretary of the US Department of Health and Human Services transmits her/his recommendation to the Drug Enforcement Administration (DEA) within the Department of Justice (DOJ). Since the spring of 2016, the schedule recommendation by the Department of Health and Human Services must be accepted and finalized by the DOJ/DEA within 90 days unless there is a compelling basis for placement in a different schedule (U.S. Congress, 2015). Finalization of the scheduling action will follow the standard federal rulemaking process (U.S. Food and Drug Administration, 2015; U.S. Office of the Federal Register, 2011).

The scientific assessment of the abuse potential (also commonly referred to as "abuse liability" and "addiction potential") is based on the scientific evaluation of substances going back to the early twentieth century search for less abusable analgesics (Jasinski et al., 1984). By the 1960s such evaluations included stimulants, sedatives, and psychedelics. This science and its methods of assessment, along with other considerations including population level public health impact, were brought together in the 1970 CSA in the form of 8 specific factors for the assessment of what was then termed "abuse potential." That term recognized that problematic use of substances could occur in people who were not physiologically dependent or addicted, and by drugs (e.g., cocaine, cannabis, LSD and psilocybin) for which it was unclear (at the time) if they posed a physiological dependence risk.

Analysis of all 8 factors is required to guide the FDA and DEA recommendations for CSA scheduling of approved medicines (Drug Enforcement Administration, 2017a; U.S. Food and Drug Administration, 2017a). Consistent with the observations that abuse potential varies widely across substances, approved medicines can vary from control in Schedule II to Schedule V (i.e., C-II to C-V), in which C-II is for those of greatest concern (e.g., cocaine, morphine, and phencyclidine), C-V is for those of sufficient concern to warrant control but for which abuse potential appears lowest among controlled substances (e.g., low dose codeine in combination with acetaminophen, lacosamide, and pregabalin). Of intermediate concern for control is Schedule IV, which includes diazepam, mazindol and tramadol, and Schedule III, which includes dronabinol, ketamine, and nalorphine.

1.1.1 FDA is the sponsors' focal point for the NDA including its abuse potential assessment—The FDA is the focal point for abuse potential assessment, and works with the sponsor to determine the range of studies needed to enable its review of the NDA in order to determine approvability, the scheduling recommendation, and all aspects of labeling (some of which are based on the abuse potential assessment and scheduling). The NDA's abuse potential assessment submission required by FDA is comprised of 5 modules that include the sponsor's scheduling proposal and rationale in Module 1, and a summary and thorough discussion of all abuse related nonclinical and clinical data in Module 2. Modules 3, 4 and 5 include complete study protocols and data addressing chemistry, in vitro and nonhuman pharmacology, and clinical studies including the integrated summary of safety (ISS), respectively. The sponsor need not submit an 8-factor analysis but sponsors often include one in their module 1 rationale.

The present 8-factor analysis benefits from the fact that psilocybin is not a new chemical entity devoid of real world (i.e., "community") data. Rather we have been able to draw from more than a half century of research and various types of therapeutic use, as well surveillance epidemiology. However, it suffers from the fact that most of the research has not been conducted as part of a cohesive sponsored drug development program that had FDA input throughout much of development. Thus, in this review we attempt to note particular strengths and weaknesses in studies and gaps in the study portfolio that will likely need to be addressed before filing an NDA.

2 Evaluation of the abuse potential of psilocybin according to the 8 factors of the CSA

The following 8-factor evaluation of psilocybin may be considered a substantially abbreviated effort compared to the 100–200 page Module 1 and Module 2 abuse potential assessment submitted as part of a potential new drug application, though substantially more detailed than the summary 8-factor analysis that might be prepared by the FDA and published by DEA in the US Federal Register in support of their scheduling recommendations (Drug Enforcement Administration, 2002, 2013, 2014, 2017b).

2.1 Factor 1. Actual or relative potential for abuse

Although the 1970 placement of psilocybin in Schedule I impeded research, more than a half century of research, clinical experience, and surveillance provide a substantial basis for evaluating the abuse potential of psilocybin according to Factor 1 and the seven additional factors. This experience has shown that psilocybin does have a potential for abuse, with preclinical and clinical studies providing information about this potential for abuse relative to other substances, scheduled and nonscheduled.

2.1.1 Preclinical studies—Psilocybin has been evaluated in a variety of preclinical models of physical dependence and abuse potential, yielding qualitatively generally similar findings with LSD. These similarities included increased pulse, respiratory rate, and pupil diameter but no physical dependence or withdrawal (Martin, 1973). Preclinical models of abuse potential suggest weak reinforcing effects and weak stimulus generalization to substances of high abuse potential (Baker, 2017; de Veen et al., 2017; Fantegrossi et al., 2008). For example, Fantegrossi, Woods and Winger (Fantegrossi et al., 2004) evaluated the classic psychedelic compounds N,N-dimethyltryptamine (DMT), mescaline, and psilocybin in rhesus monkeys with histories of self-administering 3,4-methylenedioxymethamphetamine (MDMA), a compound which is not a classic psychedelic but which produces some overlapping subjective effects in humans (Studerus et al., 2010). As shown in Figure 1 generated reliable self-administration, none of the classic psychedelics generated reliable self-administration though during occasional sessions, animals self-administered all available doses and appeared intoxicated post-session. The study authors concluded "… the present data provide further evidence that several classic psychedelic drugs from two distinct structural classes do not reliably maintain contingent responding in rhesus monkeys. This pattern of sporadic self-administration may indicate that these compounds have weak reinforcing effects, or, alternatively, mixed reinforcing and aversive effects."

The apparent weak reinforcing effects of psilocybin and other classic psychedelics may account for why there have been relatively few nonhuman studies examining reinforcement models. In contrast, many more nonhuman research studies with classic psychedelics have used drug discrimination models. Discriminative stimulus effects refer to the ability of a drug, upon administration, to serve as a cue that can predict environmental contingencies, e.g., which of two levers will result in the delivery of a reward if pressed. Discriminative stimulus effects can therefore be thought of as the ability of the drug to be recognizable to the organism (and therefore serve as a cue). Discriminative stimulus effects are different from reinforcing effects, and have different biological bases (Johnson and Ettinger, 2000). Discriminative stimulus effects may be relevant to drug reinforcement when a test drug reliably substitutes in discrimination testing for a drug with well-established reinforcing effects, e.g., when a drug reliably substitutes for amphetamine. In such cases it is likely (although not certain) that the test drug will also be shown to be reinforcing when directly tested with self-administration procedures. Discrimination studies have strongly contributed to our understanding of psilocybin and other classic psychedelics. For example, Harris and Balster compared psilocybin to amphetamine in a rodent model for assessing behavioral and discriminative effects (Harris and Balster, 1971). They found that psilocybin served as a

discriminative stimulus but that these stimulus-control effects were weak compared to amphetamine. Schechter and Rosecrans (Schechter and Rosecrans, 1972) employed a T-maze discrimination procedure and found psilocybin and mescaline, but not amphetamine, reliably substituted for LSD in rats trained to discriminate LSD from saline. Similarly, another study found the psilocybin failed to substitute for amphetamine in rats trained to discriminate amphetamine from saline (Kuhn et al., 1974). In another study rats trained with psilocybin generalized fully to psilocin (the active metabolite of psilocybin) and to LSD but not to mescaline, which is considered a classic psychedelic of the phenethylamine-based structural class rather than the tryptamine-based structural class of which psilocybin is a member (Cunningham and Appel, 1987; Koerner and Appel, 1982). Another study, however found that psilocybin fully substituted for mescaline in rats trained to discriminate mescaline from saline (Appel and Callahan, 1989). A study in pigeons found psilocybin to fully substitute for LSD in LSD trained subjects (Jarbe, 1980).

Winter, Rice, Amorosis and Rabina (Winter et al., 2007) evaluated psilocybin and other classic psychedelics following treatment with several antagonists for specific serotonin receptor subtypes. They concluded: “the present data indicate that the stimulus properties of psilocybin in the rat are broadly compatible with those of other ergoline, indoleamine, and phenethylamine classic psychedelics. However, significant differences are apparent as well” and “psilocybin induces a compound stimulus in which activity at the 5-HT2A receptor plays a prominent but incomplete role” and “the full generalization of psilocybin to LSD and to DOM is completely blocked by the selective 5-HT2A receptor antagonist, M100907, but stimulus control by psilocybin is only partially antagonized by M100907” (Halberstadt and Geyer, 2011; Winter et al., 2007).

These studies confirm that psilocybin produces discriminative effects that do not generalize to amphetamine, and psilocybin does not substitute in amphetamine trained animals. Moreover, psilocybin discriminative effects are likely mediated by psilocin, the active metabolite produced *in vivo* by dephosphorylation of psilocybin (Passie et al., 2002). In addition, findings demonstrate that psilocybin produces weak and transient reinforcing effects that are consistent with community level observations (also see Factor 4) suggesting that the vast majority of people who have used psilocybin do not develop compulsive patterns of use. Instead, more typically individuals report only a few uses of psilocybin, consistent with a substance of low overall abuse potential. The findings also suggest a need for additional studies to better understand the mechanisms of action of psilocybin and other psychedelic substances and how these may contribute to their apparent low overall abuse potential (Baker, 2017; Hayes and Greenshaw, 2011).

2.1.2 Human abuse potential assessment.—Psilocybin has not been examined in an abuse potential study that would meet the criteria recommended by the FDA in its 2017 Guidance: Assessment of the Abuse Potential of Drugs; however, many clinical laboratory studies have been conducted since the mid-1950s in which key measures of abuse potential have been assessed. This work began at the US Public Health Service Addiction Research Center (ARC) of the National Institute of Mental Health, during the time that the methods of human abuse potential were being developed. Studies with psilocybin and LSD contributed to the development of abuse potential assessment methods, in part because it was quickly

recognized that they differed in several key respects from opioids, sedatives, and stimulants which were then emerging as prototypic substances of abuse. In contrast to these drugs, any abuse potential-related effects associated with LSD, psilocybin, and related substances appeared to be unreliable and limited to specific conditions such as time of assessment, dose, and individual, social and experiential factors. In further contrast, the predominant and most reliable effects seemed to be effects thought to limit use and abuse (e.g., fear, anxiety, dysphoria, and physical discomfort including gastrointestinal upset). Thus, a leading addiction scientist and director of the ARC, Dr. William Martin, stated the following in a 1973 review of preclinical studies of psychedelic drugs: “The abuse of LSD-like hallucinogens came as somewhat of a surprise to many of the early experimenters with these drugs” (page 149)(Martin, 1973). Nonetheless, while he did acknowledge that certain doses of LSD could produce pleasure in some volunteers (Belleville et al., 1956), Martin’s 1973 review indicated that most of the preclinical and clinical findings of the 1950s and 1960s were not indicative of a prototypic drug of abuse.

Psilocybin studies at the ARC commenced a few years following studies of LSD, with the first human reports published in 1959 by Isbell (Isbell, 1959a, b). The initial studies occurred early in the development of human abuse potential assessment research when human volunteers with histories of substance abuse were evaluated for potential euphoriant effects, which were considered predictive of abuse potential (Isbell, 1956). These studies contributed to the development of human abuse potential assessment as measures evolved to characterize not only the euphoriant effects that characterized opioids and stimulants, but also the dysphoric effects that distinguished classic psychedelics such as LSD and psilocybin. At the same time theories of addiction and addiction liability assessment were evolving from the focus on physical dependence and withdrawal that had dominated the prior few decades of opioid-focused studies to a greater focus on the acute subjective and behavioral effects of drugs that contributed to their self-administration and abuse, regardless of whether physical dependence and withdrawal were evident (Isbell, 1956; Wikler, 1961).

During the 1950s and 1960s, the ARC demonstrated that among the strongest predictors of abuse potential was the reliable and dose-related production of euphoriant effects as measured by self-reported, and observer-evaluated effects including liking of the drug, apparent pleasure, confidence, and sense of well-being (Isbell, 1956). These findings led to development of systematic approaches to the assessment of drug liking, drug type identification, and frequent physiological correlates including pupil diameter and withdrawal symptoms (Fraser et al., 1961; Jasinski and Henningfield, 1989; Jasinski et al., 1984). The methods developed have continued to be refined over the past half century and remain the foundation for human abuse potential assessment studies (Carter and Griffiths, 2009; Griffiths et al., 2003; U.S. Food and Drug Administration, 2017a).

In the early 1960s, an important addition to the study of human abuse potential was the development of the ARC Inventory (ARCI), a participant-completed questionnaire. Studies of LSD and psilocybin contributed to the development of this questionnaire and a broader understanding of abuse (Haertzen and Hickey, 1987; Haertzen et al., 1963; Hill et al., 1963). Table 1 provides more background on the ARCI and its importance in characterizing the abuse potential of LSD and psilocybin. The full ARCI contained more than 500 items,

however, 49 items or fewer were found to provide valid and reliable characterization of abuse-related qualitative effects of several categories of drugs with various subscales emerging from studies of drug administration in human volunteers. The most prominent predictor of abuse potential was the Morphine Benzedrine Group (MBG) scale that came to be accepted as an important measure of euphoria. In contrast, a scale that was derived from LSD studies, the LSD scale, came to be known as the dysphoria and psychotomimetic scale, which captured fear and anxiety and seemed to predict low abuse potential. LSD and psilocybin most reliably elevated scores on the LSD scale, but frequently also, at a certain dose and in some individuals, elevated scores on the MBG scale, but generally at a lesser magnitude than opioids and stimulants (Haertzen and Hickey, 1987; Jasinski and Henningfield, 1989; Jasinski et al., 1984).

A seminal study that was that published by Isbell in 1959 found that psilocybin produced qualitatively similar effects to LSD with spontaneously reported onset of subjective effects at about 10-15 mins following oral ingestion (Isbell, 1959a). In contrast to the initial euphoric effects that characterized opioids, stimulants, sedatives, and cannabis, Isbell found that the initial effects of psilocybin were more likely to include anxiety along with altered sensations. These effects were often followed within the next 15 min by increasingly strong anxiety, and fear, visual distortions and difficulty thinking, though some subjects experienced elation and expressed “continuous gales of laughter” (page 32). He concluded that LSD was approximately 100-150 times as potent as psilocybin on subjective effects and physiologic measures including increased pupil diameter, heart and respiratory rate, and reduced threshold of the patellar reflex, with similar time course of onset but shorter duration of effects by psilocybin compared to LSD. Additional ARC studies are described in factor 2 as they pertain to understanding the mechanisms of action of psilocybin.

2.1.3 Clinical trials relevant to abuse potential assessment since 2000.—Since 2000 there have been several clinical trials that have included measures related to the assessment of abuse potential. For example, one study (Griffiths et al., 2011) showed that all four oral doses of psilocybin examined (˜0.071, ˜0.143, ˜0.286, and ˜0.429 mg/kg) produced statistically significant increases over placebo for both the A (amphetamine) scale and LSD scales of the ARCI. The MGB scale did not significantly differ between placebo and psilocybin at any dose. Another study (Bogenschutz et al., 2015) included a short form of the ARCI. Unfortunately, the open label study was neither placebo controlled, nor did it include a positive control for comparison. Such conditions are especially important for drugs that produced mixed and weak signs of abuse potential. Nonetheless, their findings were typical of those previously observed for psilocybin and LSD. The authors observed weak elevations of both the MBG and LSD scales following oral administration of 0.3 and 0.4 mg/kg psilocybin, in volunteers with histories of alcohol dependence. Whereas these effects do not indicate substantial abuse potential, they cannot be used to rule out significant potential for abuse because in the absence of comparators, the weak MBG effect might be related to the population and other design aspects of the study. This study, like others discussed in Factor 6 (Griffiths et al., 2016; Ross et al., 2016) also documented reports of acute elevations in fear and anxiety in some patients that are predictive of low abuse potential as well as a subsequently emerging sense of contentment that is not associated with

a strong motivation to use repeatedly and chronically. It is also important to note that these recent studies have gone to further lengths to maximize the pleasantness of the physical environment and establish interpersonal rapport between participants and staff (Johnson et al., 2008) compared to the older ARC studies. Therefore, MBG scores in these recent studies might overestimate the drug euphoria that would be experienced in a less than optimal environment. As in Factor 6, the mixed acute subjective effects of psilocybin included fear, anxiety, pleasure, happiness and contentment, and thus are consistent with those of the early 1960s from the ARC, however, these studies were not designed as human abuse potential studies and the putative abuse potential related effects must be interpreted cautiously. In particular, the participants in the recent cancer trials (Griffiths et al., 2016; Ross et al., 2016) were patients with severe anxiety and or depression whose therapeutic improvements in mood were long-lasting and not necessarily reflective of abuse potential.

2.2 Factor 2. Scientific evidence of its pharmacological effect

It has been estimated that there were more than one thousand scientific and clinical studies of classic psychedelics including LSD and psilocybin published through the 1960s (Drug Enforcement Administration, 1995; Grinspoon, 1981; Grinspoon and Bakalar, 1979; Johnson and Griffiths, 2017), and several thousand more published since the 1960s (Sellers et al., 2017).

Initial conclusions drawn by ARC researchers have been replicated by others as discussed in various reviews (Johnson et al., 2008; Nichols et al., 2017). In brief, in addition to physiological and behavioral effects discussed in Factor 1, it was demonstrated that repeated dosing produces diminished effects (tolerance) and that cross-tolerance occurs between psilocybin and LSD (Abramson et al., 1960; Isbell et al., 1961), but not to tetrahydrocannabinol (THC) indicating different mechanisms of action (Isbell and Jasinski, 1969). Effects of psilocybin are qualitatively similar to those produced by mescaline, however, mescaline is less potent but longer acting (Wolbach et al., 1962). The effects of psilocin are the same as those by psilocybin except that it is more potent and shorter acting than psilocybin (Isbell et al., 1961). It is now understood that psilocybin is a pro-drug, converted by dephosphorylation to the pharmacologically active psilocin (Nichols et al., 2017; Passie et al., 2002). Strong early support for this contention was provided by data showing that although psilocin is slightly more potent than psilocybin, the ratio difference in potency between the two compounds (in both humans and nonhumans) is nearly identical to the ratio of their respective molecular weights (i.e., they are equipotent on a molecular basis) (Koerner and Appel, 1982; Wolbach et al., 1962). Isbell and Logan (1957) demonstrated that chlorpromazine administration reduced and could partially reverse the effects of LSD. Nonetheless, the pharmacology and mechanisms of action of psilocybin and LSD are similar in many respects, although psilocybin is shorter acting and at least 100 times less potent than LSD (Isbell, 1959a; Sellers et al., 2017). Research has also shown the 5-HT2A antagonist ketanserin to block most of the effects of psilocybin (Kometer et al., 2012; Kometer et al., 2013; Quednow et al., 2012; Vollenweider et al., 1998), although ketanserin does not block certain psilocybin effects including the slowing of binocular rivalry, reductions in arousal/vigilance (Carter et al., 2007), and attentional impairment (Carter et al., 2005).

More than 100 species of mushrooms, in the genus *Psilocybe*, contain psilocybin (Johnson and Griffiths, 2017; Stamets, 1996). Its agonist activity at the 5-hydroxytryptamine (HT)2A receptor appears to account partially for its behavioral effects, however, the mechanisms of action of its full range of effects have not been fully elucidated (Nichols, 2016; Winter et al., 2007). Psilocybin is a substituted indolealkylamine and with diverse serotonergically mediated effects and little affinity for dopamine D2 receptors (Halberstadt and Geyer, 2011; Passie et al., 2002). It is among the structural class of classic psychedelics based on the tryptamine structure, including an indole ring (Passie et al., 2002). Albert Hofmann, the discoverer of LSD and chemist at the Swiss Sandoz Pharmaceutical Company, isolated psilocybin from Central American mushrooms (*Psilocybe mexicana*) in 1957, and synthesized the substance in 1958 (Passie et al., 2002). Its binding to and agonist effects at 5-HT2A serotonin receptors are associated with dilation of the pupils (mydriasis), reduced threshold for knee reflex, and commonly increased heartrate and blood pressure, and feelings of nausea (Isbell, 1959a, b). Its effects on mood and feeling can include visual and auditory hallucinations and distortion of visual and auditory stimuli, altered temporal sense, and alteration of body image. Its effects have the potential to mimic psychotic states which contributed to its designation, along with LSD, as a psychotomimetic. The effects that contribute to introspection and often increased receptivity to advice and psychotherapy contributed to its use in psychotherapy, as well as to investigations by psychologists and psychiatrists in efforts to better understand the moods and states of their patients (Hofmann, 1980; Matsushima et al., 2009; Passie et al., 2002).

Studies of LSD began in the 1940s with many of the same laboratories, including Sandoz, investigating the generally similar-acting psilocybin in the 1950s and 1960s. However, as discussed above in Factor 1, caution must be made in generalizing findings, including mechanisms of action, from LSD to psilocybin and vice versa. The resurgence of research beginning slowly in the 1970s and accelerating in particular since the 1990s has been rapidly increasing the understanding of the effects and mechanisms of action of psilocybin, including its general safety and the conditions of safe use (Griffiths et al., 2008; Nichols et al., 2017).

2.2.1 Tolerance and physical dependence—Tolerance refers to decreased response with repeated administration of a drug. Tolerance to the psychological and physiological effects of psilocybin is strong. Moreover, there is cross-tolerance between psilocybin and LSD. However, physical dependence and withdrawal, which refer to adverse effects upon discontinuing repeated use of a drug, have not been documented (Abramson et al., 1956; Abramson and Rolo, 1965; Balestrieri, 1967; Isbell, 1959a; Isbell et al., 1961; Passie et al., 2002; Wolbach et al., 1962). It is plausible that the FDA would recommend that sponsors collect a more rigorous evaluation of physical dependence and withdrawal in animals consistent with its 2017 abuse potential guidance, perhaps as part of a safety evaluation of high dosages. However, it is also plausible that the FDA might not require such additional studies given that there is little evidence that psilocybin produces physical dependence and withdrawal, and the treatment protocols under investigation would not involve repeated daily dosing.

2.2.2 Toxicity—Unlike prototypic opioids and sedatives of abuse, psilocybin carries a low risk of overdose toxicity by respiratory depression or cardiovascular events or other causes of death associated with substances of abuse. The LD50 of intravenous psilocybin has been determined to be above 250 mg/kg (with 200 mg/kg killing no animals, and 250 mg/kg killing a small portion of animals (Cerletti, 1958). Its lethal dose in humans has been theoretically estimated at approximately 1000 times an effective dose (Gable, 2004), which is an amount that is likely not possible for an individual to consume when in the form of psilocybin-containing mushrooms. The authors are aware of only one documented case of acute overdose poisoning death likely caused by psilocybin (Lim et al., 2012). Specifically, a 24-year old female, who had received a heart transplant 10 years prior due to end-stage rheumatic heart disease, experienced cardiac arrest 2–3 hr after consuming psilocybin-containing mushrooms, and subsequently died. Toxicology revealed only psilocin (active metabolite of psilocybin) and THC. Thus, the only known acute fatal overdose from psilocybin appears to be in a medically compromised individual. Given psilocybin's moderate pressor effects, individuals with such serious cardiac vulnerability would be excluded from recently approved psilocybin trials and should be excluded from any potential non-research future approved clinical use.

One study examined isolated nonhuman animal organs and found no significant effect in the rat uterus or the guinea pig duodenum or seminal vesicle (Cerletti, 1958). Administering relatively large doses to waking nonhuman animals of a variety of species led to acute autonomic effects including mydriasis, piloerection, hyperglycemia, hypertonia, and pulse and breathing irregularities (Cerletti, 1958), with similar effects later observed in Rhesus macaques (Horibe, 1974; Passie et al., 2002). A micronucleus study in mice found no evidence that psilocybin administration resulted in chromosome breaking (Van Went, 1978).

Hollister reported that human administration of psilocybin resulted in decreased urinary excretion of inorganic phosphorus and reduced circulating eosinophil levels, as well as pupillary dilation and increased deep tendon reflexes (Hollister, 1961). In addition, Hollister (1961) reported on a single participant who was administered psilocybin on a daily basis for 22 days, with doses ranging from 1.5 to 27 mg per day. Before and during that course of administration, no chronic changes were observed for any metric assessed: total leukocyte count, absolute eosinophil count, hemoglobin, curea nitrogen, creatinine, glucose, serum proteins, cholinesterage activity, serum glutamic-oxaloacetic transaminase titer, cholesterol and EEG tracing. Gouzoulis-Mayfrank et al. found that human psilocybin administration resulted in no change in cortisol, prolactin, or growth hormone (Gouzoulis-Mayfrank et al., 1999). Johnson et al. found that in a within-subject, double-blind, placebo-controlled study, oral psilocybin (0, ~0.071, ~0.143, ~0.286, and ~0.429 mg/kg) caused headaches which were dose-dependent in terms of incidence, duration, and severity (Johnson et al., 2012). Headaches had delayed onset relative to subjective drug effects, were transient, and ceased within 24 hr of psilocybin administration. Although mechanisms response for these delayed onset headaches are not known, one possible mechanism is nitric oxide release.

2.2.3 Pharmacodynamics—The acute effects of psilocybin have been studied in animals and humans over a broad range of doses over several decades (Isbell et al., 1961; Johnson et al., 2008; Nichols et al., 2017; Wolbach et al., 1962). Like other classic

psychedelics, the acute psychological effects following psilocybin administration are varied and often intense, although strongly dose-dependent and dependent on the interpersonal and physical environment (Griffiths et al., 2011; Hasler et al., 2004; Johnson et al., 2008). These psychological effects often include perceptual changes that are primarily visual but can also include synesthesia across sense modalities, emotional changes in which both positive and negative emotions can be far more intense than normal, cognitive changes that can include alterations in time perception, and an introspective focus on personal history, life relationships and circumstances, and changes in sense of self (Johnson et al., 2008). In a retrospective analysis of 409 psilocybin administrations to 261 healthy participants by a single research group, a few interpersonal factors among many were found to influence psilocybin response (Studerus et al., 2012). Specifically, high trait absorption scores, being in an emotionally excitable and active state before administration, and having fewer recent psychological problems all predicted pleasant and mystical-type effects, while high trait emotional excitability, younger age, and a PET imaging setting, all predicted unpleasant or anxious effects (note that pleasant and unpleasant effects within the same session are not mutually exclusive).

The early studies by Isbell and colleagues documented the time courses of onset of autonomic and psychological effects, generally beginning within 30 min of oral ingestion, peaking within 1–2 h, and subsiding over the next few hours, with a duration of action shorter than those produced by LSD and mescaline (Wolbach et al., 1962). Since 2000, several studies have been conducted in which the pharmacodynamics have been evaluated over multiple measures and doses. Hasler et al. investigated the acute psychological and physiological effects of oral psilocybin in a double-blind, placebo-controlled study in healthy volunteers at dose of 0, 0.045, 0.115, 0.215, and 0.315 mg/kg administered in a cross-over design at intervals of at least two weeks (Hasler et al., 2004). Measures included cardiovascular variables, plasma concentrations of a several hormones, and several measures of mood, subjective response and behavioral performance. Blood samples were collected pre-dosing and at 105 and 300 min post-administration. Blood pressure was measured 30 min pre-dosing and at 5, 30, 60, 90, 120, 165, and 210 min post-administration. Electrocardiograms (EKG) were continuously monitored for 24 hr. The main findings were orderly dose- and time-dependent effects that were significantly altered at many measures and timepoints. Subjective effects began to onset about 20–40 min post-administration, peaking at about 60–90 min and diminishing over the next 60–90 min. One subject became markedly anxious at the 0.315 mg/kg dose and his anxiety gradually subsided to complete resolution within 6 hr after drug administration. No significant changes were observed in EKG or body temperature, but prolactin, thyroid-stimulating hormone, adrenocorticotropic hormone, and cortisol were increased by at least the 0.315 mg/kg dose. Another dose effect study of psilocybin ranging into higher doses examined 0, ˜0.071, ˜0.143, ˜0.286, and ˜0.429 mg/kg using a placebo-controlled, double-blind, crossover design (Griffiths et al., 2011). Sessions were 1 month apart, and a 14-month follow-up was conducted. Acute psychological effects largely replicated those shown in the earlier study, with time course data showing orderly dose- and time-related effects. In addition, this study found that 39% of participants reported extreme anxiety/fear for at least one of the two highest doses. End of session data showed psilocybin caused significant dose-related increases in mystical

experience using the Mystical Experience Questionnaire. Moreover, a month after sessions, the experiences associated with the two highest doses were rated as having substantial personal and spiritual significance. Participants attributed improvements in attitudes, mood, and behavior to the two highest doses. At the 14-month follow-up, such ratings were largely unchanged from ratings made a month after each session. Improvements in attitudes, mood, and behavior were also observed in dose-blinded community members who had regular contact with participants.

More recently, two clinical trials discussed below in Factor 6 (Griffiths et al., 2016; Ross et al., 2016) also documented the time course of several physiological, mood and behavioral variables. However, persisting for far longer than these acute effects were the therapeutic effects. Specifically, both studies showed that psilocybin caused significantly and clinically significant reductions in symptoms of depression and anxiety lasting at last 6 months after psilocybin administration. Griffiths et al. studied patients with clinical anxiety and depression related to their life-threatening cancer diagnoses (Griffiths et al., 2016). Informed by data from previous psilocybin dose effects studies (Griffiths et al., 2011; Hasler et al., 2004) they compared a moderately high dose (~0.314 or ~0.429 mg/kg) to a dose sufficiently low that it was expected to be devoid of therapeutic effects (~0.014 or ~0.043 mg/kg), using a randomized, double-blind, cross-over counterbalanced design. The two doses were administered 5 weeks apart, and participants returned for 6-month follow-up. Measures of mood, attitudes, and behaviors were self-reported by participants and rated by staff and community observers throughout the study. On drug administration days, research staff were present with the patients continually during the approximately 7–8 hr long experimental session that included a battery of physiological, subjective and behavioral measures 10 min before capsule administration, repeated 30, 60, 90, 120, 180, 340, 300, and 360 min after oral capsule administration. As shown in Figure 2, there were significant dose and time-related effects on most measures including non-clinically severe increases in heart rate and blood pressure, and observer-rated anxiety, nausea, joy/intense happiness, peace/harmony, psychological discomfort and physical discomfort, but no serious adverse events attributed to psilocybin. Ross et al. used a largely similar design with a moderately high dose of psilocybin (0.3 mg/kg) being administered in one session, and a comparison compound administered in another session, with the exception that the comparison compound was niacin rather than a very low dose of psilocybin (Ross et al., 2016). Largely similar acute effects were reported, and no serious adverse effects were attributed to psilocybin.

2.3 Factor 3. Current scientific knowledge regarding drug

Psilocybin is a phosphate derivative of N,N-dimethyltryptamine that is typically is observed in concentrations ranging from 0.1 to 1.5% at least ten species of the *Psilocybe* genus of mushrooms, and in some species of other genera (Stamets, 1996). Virtually all illicit use is in the form of mushrooms, including dried and fresh mushrooms. They are often eaten whole, with or without food, but can also be heated in water to produce an active aqueous extraction (a “tea”), or powdered and consumed in capsules (if dried) (Stamets, 1996). Cultivated psilocybin-containing mushrooms have been shown to vary in psilocybin content by a factor of 4, while “street samples” of psilocybin-containing mushrooms have been shown to vary in psilocybin content by an astonishing factor of 10 (Bigwood and Beug,

1982). These wild variations in psilocybin content, combined with the variations in methods for consumption described above, suggest that dosing is not well controlled in typical illicit use. This contrasts with approved studies that administer known doses of psilocybin. There have been occasional reports of intravenous injection psilocybin in research (Carhart-Harris et al., 2016b; Petri et al., 2014; Schartner et al., 2017; Waugh, 2016) although we are aware of no reports of illicit use of psilocybin by injection.

There has been considerable progress elucidating the effects and mechanisms of action of psilocybin in animal and human studies. It is well-established that psilocybin, like other classic psychedelics, has agonist or partial agonist activity at 5-HT2A receptors (Nichols, 2016). Carbon 14-label psilocybin studies revealed that approximately 50% of orally ingested psilocybin is absorbed and rapidly systemically distributed. The isotope is distributed almost uniformly throughout the whole body. Studies of metabolites by Holzman and Hasler (Hasler, 1997; Holzmann, 1995) reported by Passie et al. (Passie et al., 2002), found four metabolites: d 4-hydroxy-N,N-dimethyltrypt-amine (Psilocin); d 4-hydroxyindole-3-yl-acetaldehyde (4H1A); d 4-hydroxyindole-3-yl-acetic-acid (41-IIAA); and d 4-hydroxytryptophol (41-IT), with a first hepatic bypass effect leading to extensive conversion to psilocin within 30 min. This corresponds to the beginning of physiological and psychological effects in the time course described below. Passie et al. (2002) reported that psilocin levels peak at about 50 min post oral administration and then slowly decline over the next 5 hr, again roughly corresponding to physiological and psychological effects, for a half-life estimated at 163 ± 64 min orally (Passie et al., 2002; Sellers et al., 2017).

Considerable progress has been made in recent years to understand the mechanisms of psilocybin's therapeutic effects. Resting state function magnetic resonance imaging shows that psilocybin administration acutely alters brain network activity. This includes decreased connectivity within the default mode network, which is a system of brain regions that supports internal focus (Carhart-Harris et al., 2012; Johnson and Griffiths, 2017). However, there is no well-documented theory about how such acute effects, lasting only hours, lead to therapeutic benefits lasting months and possibly a year or more. It has been suggested that the acute destabilization of brain networks by psilocybin (which may stem from receptor level effects via amplification of neuronal avalanches) may provide the opportunity to alter brain network activity in a persisting fashion (Johnson and Griffiths, 2017; Nichols et al., 2017). Such a mechanism has been suggested as consistent with the evident importance of the appropriate context and importance of psychotherapy in the therapeutic benefits of both psilocybin and LSD (Hofmann, 1980; Johnson et al., 2008; Johnson and Griffiths, 2017). That is, the acute effects of psilocybin in altering brain network dynamics may set the occasion for such networks to re-establish themselves in altered ways after the conclusion of acute effects; the overall context and the non-drug therapeutic aspects of the intervention may play a role in shaping such re-established networks.

As reviewed by Nichols et al. (2017), it is now known that serotonergic-acting psychedelics, including psilocybin, have anti-inflammatory effects and may have efficacy in treating some inflammatory diseases. They observed that inflammation of the brain "has been linked to several psychiatric disorders including depression, addiction, and neurodegenerative disorders such as Parkinson's and Alzheimer's disease." Insofar as elevated serotonin levels

are associated with inflammation it is plausible that psilocybin has anti-inflammatory effects in the brain, possibly involving serotonergic systems that contribute to its therapeutic effects (Nichols et al., 2017).

2.4 Factor 4. History and current pattern of abuse

Table 2 provides a summary overview of psilocybin and psilocybin-containing mushrooms in cultures dating back at least 7 millennia. From the perspective of understanding the abuse potential of psilocybin it is important to note that the history of psilocybin use has primarily involved naturally occurring psilocybin containing mushrooms. Use of these mushrooms by non-indigenous individuals in the US and elsewhere began soon after Wasson's discovery of mushroom ceremonies in the late 1950s (Stevens, 1987). An exception was the brief distribution of a pure psilocybin containing drug product branded as Indocybin® as an adjuvant to psychotherapy or a tools in experimental psychiatry, free of charge for a few years in the early 1960s by the Swiss Sandoz pharmaceutical company (Lee and Shlain, 1992; Passie et al., 2002). In those days this general approach was permitted for drugs that were not approved for therapeutic use (Bonson, 2018). Nonetheless, research on psychedelic substances began to slow in 1962/1963 when US scientists were required to seek federal approval for evaluations of psilocybin or LSD (Stevens, 1987).

2.4.1 United States national surveys—Various national agencies monitor a broad range of substance use related behaviors, effects, concomitants and treatment seeking. Together, these characterize the prevalence and trends and effects related to various substances geographically and demographically. A brief summary of the major surveillance systems follows.

Treatment Episode Datasets (TEDS): TEDS is an annual record of U.S. substance abuse treatment admissions. The methods of the survey and data collection are described elsewhere (Substance Abuse and Mental Health Services Administration, 2017a). An estimate of treatment for psilocybin use disorder specifically cannot be assessed because it has not emerged as a sufficiently large cause of substance use disorders to warrant its own category, thus, the TEDS assesses a composite category termed "hallucinogens," which includes LSD, DMT, "STP" (2,5-dimethoxy-4-methylamphetamine or DOM), mescaline, peyote, psilocybin, and other (unnamed) "hallucinogens". Common substances sometimes considered to be "hallucinogens" but which are included in other TEDS categories (rather than the "hallucinogen" category) are MDMA and phencyclidine (PCP). As shown in Table 3 for all years from 2005 to 2015, "hallucinogens" were consistently reported as the primary substance of abuse in 0.1% of all admissions aged 12+ years. In 2015 those who reported "hallucinogens" as their primary substance of abuse at admission were 74.9% male and – on average – 28 years of age, and 43.6% had not used "hallucinogens" in the past month (only 25.9% had used daily in the past month). To provide some perspective we include TEDS data for opiates, cocaine and alcohol. Together these data show that among substances of abuse, treatment seeking for the entire category of "hallucinogens" constitutes a very small fraction of reports to TEDS with no evidence of increasing trends over the last decade of reports

Drug Abuse Warning Network (DAWN): The DAWN, which monitored U.S. drug-related visits to emergency departments, was discontinued after 2011. The methods and its scope of data collection are described elsewhere (Substance Abuse and Mental Health Services Administration, 2013). As shown in Table 4, from 2004 to 2011, the data suggest an increasing trend in psilocybin-related emergency department (ED) visits. However, the signal is so small, compared to "pain relievers," cocaine, and alcohol that an increase from 0.2 to 0.4 of all ED visits must be interpreted with caution. In terms of rates, psilocybin-related ED visits increased from 1.0 per 100,000 population in 2004 to 1.9 per 100,000 population in 2011.

National Survey on Drug Use and Health (NSDUH): The NSDUH is an annual survey of substance use and mental health issues in US civilians ≥ age 12. Methods for some NSDUH items changed in 2015, necessitating trend breaks in some cases. However, items related to "hallucinogens" were not modified. As shown in Table 5, between 2009 and 2015, lifetime use of psilocybin was consistently reported by about 8.5% of NSDUH respondents aged 12 and older, with a low of 8.1% (in both 2011 and 2012) and a high of 8.7% (in 2013). The reported lifetime use rate in 2015 was 8.5%. The methods of the survey, including specific questions are described in detail elsewhere (Substance Abuse and Mental Health Services Administration, 2017b).

Monitoring the future (MTF): The MTF is a survey of substance use and attitudes of U.S. secondary school students, college students, and young adults. It does not ask its participants about prevalence of psilocybin use; however, the survey does ask about "hallucinogens", which is broken down into LSD and "hallucinogens" other than LSD. The two substances most commonly identified in the class "hallucinogens" other than LSD, has been psilocybin or "shrooms." From 2006 to 2011, lifetime prevalence of high schoolers using hallucinogens other than LSD (of which psilocybin/shrooms comprise the largest proportion), stayed relatively stable around 5.0%, but from 2011 to 2016, lifetime prevalence has decreased from 4.9% to 3.0%. Past year use among high schoolers mirrored this trend, staying relatively stable from 2006–2011 (around 3.0–3.3%) and declining from 3.1% in 2011 to 1.8% in 2016. Among college students, lifetime prevalence of use of "hallucinogens" other than LSD has steadily declined in the past 10 years from 10.1% in 2006 to 6.6% in 2016. Among college students, past year prevalence for "hallucinogens" other than LSD has also steadily declined from 5.4% in 2006 to 3.0% in 2016. Among young adults aged 19–28, lifetime prevalence for "hallucinogens" other than LSD declined from 14.9% in 2006 to 10.6% in 2016. Among young adults aged 19–28, past year prevalence for "hallucinogens" other than LSD has declined from 3.8% in 2006 to 3.0 in 2016.

National Forensic Laboratory Information System (NFLIS): The NFLIS system of the DEA is based on results from drug chemistry analyses conducted by state, local and federal forensic laboratories, from drug seizures by law enforcement. It is not a measure of human use, abuse, overdose or effects but rather is intended to provide information about what substances are being found in drug seizures (also known as "busts" or "raids") across the country (Drug Enforcement Administration Diversion Control Division, 2016). As shown in Table 6, the estimated number of total drug reports for psilocin/psilocybin has slightly

declined from a high of 0.30% of total drug reports in 2010 to staying relatively stable from 2013 to 2015 (0.27% of all drug reports in 2013 and 0.26% of all drug reports in 2014 and 2015), however these rates are so small in comparison to other substances that interpretation must be made with caution.

American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS): As shown in Table 7, from 2007 to 2015, there were 5559 case mentions of psilocybin and psilocin reported to the National Poison Data System (NPDS). A mention indicates that the substance was associated with, but not necessarily the cause of, a reported suspected poisoning. Of these 5559 mentions, there was one death, in 2012. Whether this death was the result of psilocybin use or other concomitant drug use is unknown. Case reports mentioning psilocybin and psilocin have decreased from 773 reports in 2007 to 473 in 2015.

2.4.2 A Note on "Microdosing"—

Psychedelic "microdosing," which involves use of very low, sub-perceptual, doses of psychedelics, has recently received attention in popular press articles and books (Fadiman, 2011; Koebler, 2015; Malone, 2016; Waldman, 2017). Although popular attention to microdosing is relatively new, Albert Hofmann discussed the medical potential of using very low doses of LSD for antidepressant effects (Horowitz, 1976) as early as 1976. Six percent of individual responding to a drug-related survey indicated having microdosed with LSD at least once in their lifetime (Global Drug Survey, 2017). However, nothing is currently known about the population-level prevalence of psychedelic microdosing, nor about microdosing of psilocybin mushrooms among psychedelic users. Given the substantial variability in psilocybin-content in mushrooms (Bigwood and Beug, 1982), one risk of microdosing with mushrooms is accidentally consuming a higher psilocybin dose than intended, resulting in strong and possibly overwhelming psychological effects in a dangerous or otherwise problematic environment, for example, while driving or working.

2.5 Factor 5. The scope, duration, and significance of abuse

There is an extensive history that provides important insights concerning patterns of psilocybin, LSD and other classic psychedelic use, abuse, and place in culture in the US and globally. Unlike, LSD, psilocybin is not a new molecular entity but rather is a naturally occurring substance that has been used ritualistically for at least hundreds and likely thousands years in Central and South America and possibly Africa and Europe (Akers et al., 2011; de Borhegyi, 1961; Lowy, 1971; Samorini, 1992; Schultes, 1969; Schultes et al., 2001; Truttman, 2012), with an apparently revered place in many cultures through history (Schultes et al., 2001). By way of contrast, alcohol, cocaine, opioids, and tobacco also have histories of use dating thousands of years, but these substances were recognized as addicting and harmful to the lives of many users for centuries (Corti, 1931; Crocq, 2007; Lewin, 1998; Rush, 1808; Terry and Pellens, 1970). As discussed in the foregoing citations, many users of these classic substances of abuse developed patterns of daily use that interfered with social and occupational functioning and caused harm to users. Moreover, with these drugs abstinence often came with great difficulty and was sometimes associated with sickness.

Such sickness was eventually recognized as part of a withdrawal syndrome that contributed to the persistence of chronic daily use (Koob and Le Moal, 2006; O'Brien, 2011).

In contrast, whereas many experts (Gable, 1993, 2004) and expert organizations including NIDA and the DEA recognize psilocybin as a drug of abuse, they universally differentiate it from drugs that cause dependence/addiction and carry a high risk of overdose and harm. For example, NIDA Drug Facts website describes LSD and psilocybin type classic psychedelics as not addicting in contrast to NMDA antagonist phencyclidine (PCP) which may be considered an addicting "hallucinogen," broadly speaking. See Table 1.

The characterization of psilocybin as a substance with high abuse potential is based largely on social lore, sensationalized media coverage, and misinformation and misunderstanding about the actual risk of dependence and harms during the 1960s. This coincided with nonmedical use of classic psychedelics, primarily LSD, by the public in the 1960s (British Psychological Society, 2014; Costandi, 2014; Hofmann, 1980; Penner, 2015; Pollan, 2015). There is no question that such use involved motivation for intoxicating effects, and frequently involved co-administration of other substances. Furthermore, even though medical use by experienced practitioners had shown these drugs to be remarkably safe, use in the population for nonmedical reasons, often in high doses, in combination with other drugs, and in unsafe environments, led to highly sensationalized adverse consequences that contributed to the characterization of these substances as dangerous and highly abusable and ultimately in their placement in Schedule I of the CSA when it was codified in 1970. See further discussion in Belouin and Henningfield in this journal issue and Hofmann, 1980.

Scientific and medical studies, and US national surveillance systems yield a different characterization of psilocybin use, abuse, and risks than the 1960s media accounts as summarized in this factor and other factors. The scientific evidence confirms that there has been abuse and supports regulation as a controlled substance, however, that actual risk of dependence and harm associated with psilocybin has been estimated to be among the lowest of all major substances of abuse and dependence over the past several decades by several expert analyses, and lines of evidence evaluated in this factor and other factors of the CSA. For example, in a comparative overview of the dependence potential and acute toxicity of psychoactive substances, Gable concluded that psilocybin carried a lower risk of dependence than caffeine and among the lowest risks of death of all major substance abuse categories including cannabis (Gable, 1993). In a subsequent analysis using different methods Gable again found that psilocybin was amongst the least physiologically toxic drugs (Gable, 2004).

Similarly, Nutt, King, Saulsbury and Blakemore developed an instrument to assess drug harms and misuse that considered "physical" and "social" harm and dependence risk, and had a group of UK drug experts rank a large group of licit and illicit drugs (Nutt et al., 2007). Heroin, cocaine, sedatives and alcohol were ranked highest in overall harm. Although psilocybin was not specifically evaluated, the related drug LSD was ranked among the drugs with the lowest harm. This general approach was extended to use a more advanced decision-making approach, and included 16 specific criteria for evaluation by experts in the United Kingdom (Nutt et al., 2010). Alcohol was ranked most harmful with an overall harm score of 72 out of a possible 80, followed by heroin (overall harm score of 55 out of 80) and crack

cocaine (overall harm score of 54 out of 80); the lowest overall score, as show in Figure 3, was assigned to “mushrooms, with an overall harm score of 6 out of 80.

A large survey of 1501 UK drug users (Morgan et al., 2010) assessed ratings of harms for the drugs previously examined by the UK drug experts in Nutt et al. (Nutt et al., 2007). Although psilocybin was not assessed, LSD was ranked relatively low in harm among other drugs (Morgan et al., 2010). In a similar study (Carhart-Harris and Nutt, 2013), experienced drug users rated harms to “self” and to “others.” The ratings by substance users and experts were overall similar, placing LSD among the lowest in harm to self and others with psilocybin-containing mushrooms receiving the lowest ratings (Carhart-Harris and Nutt, 2013). A study utilizing Dutch experts, using a framework based on that developed by Nutt and colleagues (Nutt et al., 2007), similarly concluded psilocybin-containing mushrooms to be the least harmful of all licit and illicit drugs examined, both to the individual and to the population (van Amsterdam et al., 2010). In turn, similar findings were obtained by 40 European Union addiction experts who scored 20 drugs on 16 factors related to harm (van Amsterdam et al., 2015). As shown in Figure 4, harm ratings at the population and individual level were among the lowest for “magic mushrooms” among all substances that were evaluated.

Lending confidence to these various assessments of drug harm rankings is the remarkable correspondence among them. Specifically, using the drugs in common between studies, the correlation between Nutt et al. (2007) expert rankings and the Nutt et al., (2010) expert rankings were strong (Pearson’s r = 0.70) despite methodological differences (Nutt et al., 2010). The van Amsterdam et al., (2010) Dutch expert rankings and Nutt et al., (2010) UK expert rankings were also strongly correlated (Pearson’s r: individual harm: 0.80, population harm: 0.84). The correlation between the UK drug user rankings in the Morgan et al. (2010) study and the UK expert rankings in Nutt et al. (2007) were strong (Pearson’s r = 0.90) (Morgan et al., 2010). The correlation between the UK drug user rankings in the Carhart-Harris et al. (2013) study were strongly correlated with both of UK expert rankings (Nutt et al., 2010: User harms Spearman’s rho = 0.90, harm to others Spearman’s rho = 0.76) and the Dutch expert rankings (van Amsterdam et al., 2010) (Individual level: Spearman’s rho = 0.93; Population level: Spearman’s rho = 0.94) (Carhart-Harris and Nutt, 2013). The rankings of European Union addiction experts showed remarkably high correlations to UK experts (Nutt et al., 2010; van Amsterdam et al., 2015) (Overall harm: Pearson’s r = 0.99). Collectively, these studies suggest strong international, cross-laboratory consensus, across academics, clinicians, and drug users themselves, regarding the relatively low harm potential of psilocybin compared to other drugs of abuse.

An evaluation of the harm-potential of psilocybin-containing mushrooms use, sanctioned by the Minister of Health of the Netherlands, “concluded that the physical and psychological dependence potential of magic mushrooms was low, that acute toxicity was moderate, chronic toxicity low and public health and criminal aspects negligible” (van Amsterdam et al., 2011). Further, the evaluation concluded that while “the use of magic mushrooms is relatively safe as only few and relatively mild adverse effects have been reported,” the most harmful instances of use tended to involve the combination of other drugs including alcohol with mushrooms, and suboptimal settings such as the absence of a sober companion.

An important evaluation of the comparative epidemiology of dependence across a broad range of substances, including “psychedelics” was performed by Anthony, Warner and Kessler using data from the National Comorbidity Survey (Anthony et al., 1994). With respect to the rank ordering of the risk of transition from “drug use” to “dependence” they concluded as follows: “For both men and women, and for all but the oldest age group of drug users, tobacco and heroin were top ranked; psychedelic drugs (defined in report as “e.g., LSD, peyote, mescaline” which presumably would have included psilocybin) and inhalants were at the bottom.” (Anthony et al., 1994). The inhalant results are unfortunately difficult to interpret because “inhalant” included compounds that widely varied in mechanism of action and related harms, from volatile solvents such as gasoline to nitrous oxide.

2.6 Factor 6. Risk to public health

Risks to public health can be estimated by a variety of approaches that help capture consequences of use among users and to nonusers. Carbonaro et al. (2016) reported on an online survey of psilocybin users about their single most psychologically difficult or challenging experience after consuming mushrooms. Eleven percent reported putting her/himself or others at risk of physical harm. Greater estimated dose, duration and difficulty of the experience, and lack of physical comfort and social support, were all related to increased risk. Approximately three percent reported behaving in a physically aggressive or violent manner, and the approximately three percent reported receiving medical help. Including only individuals whose reference psilocybin exposure occurred more than a year before survey completion, approximately eight percent reported seeking treatment for persisting psychological symptoms. Three of the respondents reported their psilocybin use to be followed by the onset of enduring psychotic symptoms. Three respondents reported attempting suicide.

As discussed in Factor 2, the risk of overdose poisoning by psilocybin is low due to its low physiological toxicity. In addition, it is possible that the often undesirable effects of high doses of psilocybin (Griffiths et al., 2011; Johnson et al., 2012), combined with large variability in the psilocybin-content of mushrooms (Bigwood and Beug, 1982) may lead many users to be cautious about dosing. On the other hand, its well documented sensory altering and impairing effects suggest a potential concern for the safety of users and others. By way of contrast, more than 10,000 or almost one third of all driving-related deaths in 2015 involved alcohol (Centers for Disease Control and Prevention, 2017), in addition to more than 2000 alcohol overdose poising deaths (Centers for Disease Control and Prevention, 2015), and nearly 80,000 alcohol related liver disease deaths (National Institute on Alcohol Abuse and Alcoholism, 2017). Recent trends suggest that an increasing fraction of highway motor vehicle accidents involve substances other than alcohol, including prescription drugs and possibly cannabis. The exception to this trend appears to be the category of “hallucinogens” (Rudisill et al., 2014). A plausible explanation is that the acute effects of classic psychedelics are so disrupting that persons under the influence are less likely to drive than those who are under the influence of intoxicating, sedating, and inhibition releasing substances that are more commonly associated with traffic accidents and fatalities. Another plausible contribution is the fact that psilocybin is typically used far less

frequently than these other drugs which more readily lead to daily use and use disorders; therefore, there are fewer instances of drug intoxication involving driving and therefore fewer driving-related deaths.

Nonetheless, concerns about the safety of users and others have been voiced since early research with psilocybin and other psychedelics. Therefore, the relative rarity of apparent cases of classic psychedelic involved deaths does not mean that this should be of no concern (de Veen et al., 2017; Hofmann, 1980). Thus, despite an apparently low risk of addiction and physiological toxicity, there is concern about abuse because of potential adverse effects, including panic reactions, possible precipitation of enduring psychiatric conditions (i.e., psychotic disorders), and long-lasting visual perceptual disturbances. Importantly, these risks can be minimized by control of dose, setting, patient selection and other factors (Carhart-Harris and Nutt, 2013; de Veen et al., 2017; Johnson et al., 2008). What is reassuring, and at odds with one of the conditions for CSA Schedule I control ("There is a lack of accepted safety for use of the drug or other substance under medical supervision.") is that decades of experience and recent clinical research demonstrate that psilocybin can be used safely under medical supervision and the conditions of safe use are increasingly well-defined (Griffiths et al., 2016; Johnson et al., 2008; Ross et al., 2016).

It is likely that in the approval of psilocybin for therapeutic application, the FDA would not simply assume low risk, but rather would require that such serious but mitigatable concerns warrant a REMS to contribute to safe use and minimize unintended negative effects (U.S. Food and Drug Administration, 2015). Approval of drugs with REMS anticipates the likelihood that emerging clinical experience, further research, and the relatively high level of oversight and data collection provided by the REMS can support expansion of the conditions and indications for use and result in modifications of the REMS itself, as was the case for sodium oxybate (Xyrem®), the medication whose active pharmaceutical ingredient is the controversial substance commonly known as GHB (Carter et al., 2009; Carter et al., 2006; Johnson and Griffiths, 2013; McCormick et al., 2009; The Medical Letter, 2006; Wang et al., 2009). Data important in understanding the safety, mechanisms of action, and potential future indications for psilocybin-assisted treatment have included the treatment of substance use disorders (Bogenschutz et al., 2015; Garcia-Romeu et al., 2014; Johnson et al., 2014; Johnson et al., 2017; Johnson and Griffiths, 2017; Johnson et al., 2012; Nichols et al., 2017; Sessa and Johnson, 2015; Tupper et al., 2015), obsessive-compulsive disorder (Schindler et al., 2015), and cluster headaches (Matsushima et al., 2009; Sewell et al., 2006).

Ideally REMS are designed with knowledge gained from clinical trials to provide a basis for a plan that will contribute to beneficial effects and mitigate the risk of undesired effects. In this case there is knowledge that goes back to the 1950s efforts of Sandoz to ensure safe use by health care providers and the 21st century clinical trials have carefully designed and documented their programs to minimize unintended consequences. Furthermore, history and clinical research indicate that adverse events are not random but are related to controllable factors that can be addressed in labeling and by the requirement of elements to assure safe use (ETASU) of REMS that would likely be required by the FDA given (a) the 1960s history that did include problems, and (b) the apparent ability to minimize problems by following

protocols employed in clinical research. In fact, information that would contribute to the development of a REMS is already emerging from recent clinical safety and efficacy trials.

2.6.1 Potential public health benefits—Risk to public health and overall public health impact must include consideration of benefits in order to provide a balance risk to benefit analysis. This concept has received increasing attention from the FDA in recent years. For example, in the 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) Section X, is entitled "Enhancing Benefit-Risk Assessment in Regulatory Decision-Making." This section required the FDA to "develop a five-year plan to further develop and implement a structured benefit/risk assessment in the new drug approval process" and "An evaluation plan to ascertain the impact of the benefit-risk framework in the human drug review process. The evaluation will consider the utility of the framework in facilitating decision-making and review team discussions across disciplines, risk management plan decision-making, training of new review staff, and communicating regulatory decisions. In particular, the evaluation will consider the degree to which the framework supports or facilitates balanced consideration of benefits and risks, a more consistent and systematic approach to discussion and decision-making, and communication of benefits and risks." (U.S. Food and Drug Administration, 2012). The plan included holding two public workshops addressing benefit-risk considerations in drug regulation, one of which was held September 18, 2017 (U.S. Food and Drug Administration, 2017b).

The importance of public health benefits in drug scheduling decision-making is not new but its prominence seems to be increasing and in fact, the standard for evaluation of new tobacco products and for potential approval of some harm reduction tobacco products as "Modified Risk Tobacco Products" invokes a public health standard and not an efficacy standard by the 2009 Family Smoking Prevention and Tobacco Control Act (U.S. Congress, 2009). Nicotine is a drug that meets criteria for placement in Schedule III of the CSA (if marketed as a drug but not in the form of tobacco products which are exempted from CSA scheduling along with alcoholic beverages by the CSA) but the potential public health benefits of nicotine were prominent in the decision by the FDA not to recommend scheduling upon approval of nicotine gum in 1985, and in 1996 not to recommend scheduling of a nasal nicotine product that clearly met criteria for such control (Henningfield et al., 2016; U.S. Food and Drug Administration, 1996). Similarly, public health considerations were prominent in the FDA's resistance to reschedule low dose hydrocodone plus acetaminophen products from Schedule III to Schedule II (Anson, 2014; Coleman, 2015).

In this context, it is important to recognize the potential public health benefits of psilocybin and to avoid unduly restrictive scheduling that would pose an unnecessary barrier to potential life-saving and public health enhancing access. For example, placement in Schedule II is intended to pose high barriers to patient prescribing by health care providers and access by patients, and this was a consideration in advocacy by the FDA, pain patient advocacy organizations, and many people with pain in sustaining the low dose acetaminophen combination form of hydrocodone in Schedule III as discussed above (Coleman, 2015).

As discussed in the summaries of analyses of Factors 4 and 5 in this article and earlier in this section, the overall risks to public health posed by illicit psilocybin are low compared to most scheduled drugs and certainly lower than most Schedule II and III drugs. Clinical studies of psilocybin suggest that the public health risk of an approved medicine would be lower still due to the restrictions on its access imposed by distribution only through pharmacies and potentially at least initially limited to a single central pharmacy provider if that was recommended as part of its REMS program (Griffiths and Johnson, 2015).

The potential medical and public health benefits of medicinal psilocybin were demonstrated by research up until the 1960s, and with some resurgence beginning in the 1990s. The clinical development program for psilocybin as a potential medicine as for the treatment of depression and anxiety and to improve quality of life in patients with life-threatening cancer diagnoses (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016), provides more recent data, from studies that are intended to meet FDA standards for Phase 1 and 2 studies to support an eventual new drug application. In summary, Grob et al. assessed the effects of one-time psilocybin (14mg/70kg doses) using a double-blind, placebo-controlled design, with administration in a therapeutic setting in patients with life-threatening illnesses including cancer (Grob et al., 2011). There were reductions in measures of trait anxiety and depressed mood that persisted through the 6-month follow-up observation. There were no serious adverse events. Carhart-Harris et al. conducted an open label study of 10 and 25 mg doses of psilocybin administered 7 days apart in a supportive setting in patients with treatment-resistant depression. This demonstrated strong reductions in measures of depression at 1 week and 3 months by the 16-item Quick Inventory of Depressive Symptoms, with no serious adverse events (Carhart-Harris et al., 2016b).

The most rigorous study of psilocybin for treatment of depressed mood and anxiety in severely distressed cancer patients was by Griffiths et al. (Griffiths et al., 2016), as described under Factor 2. Acute effects during the sessions were described (see Figure 2). As shown in Figure 5, the therapeutic benefits of the high dose of psilocybin (~0.314 or ~0.429 mg/kg) were profound and persistent as reported by both patients and observers. The overall rates of clinician-rated therapeutic effects at 6 months were 78% for depression and 83% for anxiety. Ross et al. conducted a study that was generally similar to that by Griffiths et al., with the most important difference being the use of small doses of niacin as an active placebo instead of low doses of psilocybin (Griffiths et al., 2016; Ross et al., 2016). Ross et al. also found robust acute and sustained antidepressant effects by psilocybin. Ross et al. and Griffiths et al. have assisted a nonprofit program that has been coordinated by the Heffter Research Institute (Heffter Research Institute, 2017) and Usona Institute (Usona Institute, 2017) which are working together to sponsor the development of psilocybin for approval as a medicine by the FDA. These studies include measures of mood enhancement in patient populations that are not discussed in Factor 1 (regarding euphoriant effects) l because the relevance of persisting mood improvement in depressed and anxious patients to abuse potential is not clear (Griffiths et al., 2016).

Non-therapeutic laboratory studies of psilocybin in healthy volunteers also suggest positive persisting effects of psilocybin. Two studies administering doses of up to ~0.429 mg/kg to healthy volunteers showed increased participant-ratings of well-being or life satisfaction

(Griffiths et al., 2008; Griffiths et al., 2011) 14 months after psilocybin administration. Data pooled across these studies showed an increases in personality over a year after psilocybin administration (MacLean et al., 2011). A recent, large laboratory study examining the interactive effects of psilocybin and spiritual practices (including meditation) in 75 healthy volunteers showed high-dose psilocybin (˜0.286 and ˜0.429 mg/kg in two separate sessions) to cause significant increases in ratings of interpersonal closeness, gratitude, and life meaning/purpose 6 months after psilocybin administration, suggesting persisting improvements prosocial traits and psychological functioning (Griffiths et al., in press).

Larger, population- and cohort-based studies are consistent with findings from these experimental investigations. For example, Hendricks et al. tested the relationships of classic psychedelic use and psilocybin use per se with psychological distress and suicidality among over 190,000 adult respondents pooled from years 2008 through 2012 of the NSDUH (Hendricks et al., 2015a; Hendricks et al., 2015b). They found that lifetime classic psychedelic use was associated with a reduced odds of past month psychological distress (aOR = 0.81), past year suicidal thinking (aOR = .86), past year suicidal planning (aOR = 0.71), and past year suicidal attempt (aOR = 0.64), with these results extending to psilocybin per se. Lifetime illicit use of other drugs was, by and large, associated with an increased odds of these outcomes. Building on these findings, Argento et al. (2017) found that psychedelic drug use, broadly defined (i.e., not restricted only to 5HT2A agonists but also including MDMA) prospectively predicted a reduced likelihood of suicide ideation or attempts among 290 marginalized Canadian women (aHR = 0.40). Moreover, consistent with pilot studies of psilocybin-assisted psychotherapy for drug dependence (Bogenschutz et al., 2015; Johnson et al., 2014), Pisano et al. found that lifetime classic psychedelic use was associated with a reduced risk of past year opioid dependence (weighted risk ratio = 0.73) and past year opioid abuse (weighted risk ratio = 0.60) among over 44,000 illicit opioid users who completed the NSDUH in years 2008 through 2013 (Pisano et al., 2017). Finally, a growing literature suggests protective effects for individuals in the criminal justice system, who suffer from numerous comorbid psychopathologies including depression, anxiety, and drug dependence that exacerbate criminal behavior. Hendricks et al. found that naturalistic “hallucinogen” use predicted a reduced likelihood of recidivism among over 25,000 individuals under community corrections supervision with a history of substance involvement (aOR = 0.60) (Hendricks et al., 2014) and Walsh et al. found that naturalistic “hallucinogen” use predicted reduced arrest for intimate partner violence among 302 jail inmates (aOR = 0.62) (Walsh et al., 2016). Of course, as “hallucinogens” are a broader class of substance that includes classic psychedelics such as psilocybin in addition to other substances, these studies were not able to test the unique relationships of classic psychedelics or psilocybin in particular with criminal behavior. Toward that end, Hendricks et al. (2018) evaluated the associations of classic psychedelic use, and psilocybin use per se, with criminal behavior among over 480,000 adult respondents pooled from years 2002 through 2014 of the NSDUH. They found that lifetime classic psychedelic use was associated with a reduced odds of past year larceny/theft (aOR = 0.73), past year assault (aOR = 0.88), past year arrest for a property crime (aOR = 0.78) and past year arrest for a violent crime (aOR = 0.82). Results also were consistent with a protective effect of lifetime

psilocybin use for past year antisocial behavior. Lifetime illicit use of other drugs was largely associated with an increased odds of these outcomes.

To be clear, it is not a conclusion of this review that psilocybin or other psychedelics should currently be recommended as a general or blanket approach for the prevention of suicide or other behaviors and conditions discussed in this section. Nor is it proposed that approval of psilocybin for depression and anxiety disorders related to advanced cancer diagnosis will translate to reduced suicide or other problems at the population level in the near term, if ever. In part this is because self-selection and other factors may contribute to the population level effect. Furthermore, psilocybin and related substances can produce adverse effects that were documented by Hoffman in the 1940s and since, and the risks of such adverse events can be minimized by appropriate protocols, conditions for use, dosing and other factors. However, in the evaluation of the potential public health effects, the data suggest that psilocybin is overall more likely to contribute to public health improvement than to adversely affect public health. Taken together, the evidence suggest that, at least with respect to certain mental disorders, psilocybin appears to offer potential benefits to patients and little risk to public health (Belouin and Henningfield, 2018).

2.7 Factor 7. Psychic or physiological dependence liability

No apparent physiological dependence as evidenced by withdrawal symptoms has been documented in humans (clinical observations) or animals (laboratory studies), although tolerance has been observed (Abramson et al., 1960; Appel and Freedman, 1968; Isbell et al., 1961). For example, no withdrawal was reported following chronic psilocybin use in humans in ARC studies including a study by Isbell et al. (1961) of 19 participants that included up to 12 days of psilocybin (ascending up to 0.15 mg/kg or 0.21 mg/kg) followed by up to 13 days monitoring after termination of administration. With the exception of MDMA, which is distinct from classic psychedelics both in effects and primary pharmacological mechanism of action, the Fifth edition of the Diagnostic and Statistical Manual of the American Psychiatric Association (DSM 5) does not include a diagnosis of Withdrawal for “hallucinogens” (American Psychiatric Association, 2013). As concluded by O’Brien (2011), “Frequent, repeated use of psychedelic drugs is unusual, and thus tolerance is not commonly seen. Tolerance does develop to the behavioral effects of LSD after three or four daily doses, but no withdrawal syndrome has been observed” (O’Brien, 2011). The Isbell et al., (1961) study discussed above observed tolerance (decreased drug effect after chronic treatment) to all measured effects of psilocybin, some of which met statistical significance. Hollister reported on a single participant who was administered psilocybin on a daily basis for 22 days, with doses ranging from 1.5 to 27 mg per day, and noted strong tolerance, with minimal apparent effects, to 15 mg on day 22 (Hollister, 1961). After several weeks of abstinence the same 15 mg dose resulted in a robust and typical response, demonstrating a recovery from tolerance. Cross-tolerance occurs between psilocybin and LSD (Abramson et al., 1960; Appel and Freedman, 1968; Isbell et al., 1961).

2.8 Factor 8. Immediate precursor of substance controlled

Psilocybin is a prodrug to the active entity, psilocin, both of which are currently placed in Schedule I of the CSA.

3 Discussion

3.1 Summary and recommendation for CSA scheduling

All 8 factors and other lines of evidence taken together indicate the profile of a substance that is characterized by some level of abuse potential and potential risks. However, the findings do not support placement more restrictively than Schedule IV. The current placement in Schedule I is presently necessitated by the absence of FDA approval for a psilocybin containing medicine and Schedule I is the only Schedule into which substances of abuse can be placed that do not have an approved medical indication. However, it is the opinion of the authors of this review that the original placement of psilocybin was the result of a substantial overestimation of the risk of harm and abuse potential. The CSA stipulates that Schedule I is for substances with a high potential for abuse, lack of therapeutic approval, and that cannot be used safely in medicine. History of use and available scientific data show that the first criterion is questionable, and the third criterion is likely not true. The second of these criteria can only be negated by FDA approval of a psilocybin-containing products, but at this point the data suggest that the potential therapeutic benefits of psilocybin-assisted therapy are real, and of potential medical and public health significance.

Schedule placement is guided by an analysis of the 8 factors of the CSA that will be drafted by the FDA with input from NIDA. The 8-factor analysis contained in this review should be considered an abbreviated assessment of abuse potential as compared to what would be required by the FDA to accompany the submission of an NDA for approval of a psilocybin containing drug product. Furthermore, considerable additional study will yet be required to support the submission of a complete and reviewable NDA and its abuse potential assessment. This will include at least one major phase 3 clinical efficacy and safety trial that includes assessments relevant to abuse potential, additional Phase 1 and/or 2 clinical studies, and possibly some animal testing (Calderon et al., 2017; Heal et al., 2018; Sellers et al., 2017). Thus data yet to be collected will influence the final scheduling proposal that will be made by the sponsor and, in turn by the FDA, NIDA, and DEA. Nonetheless, considerable data from animal self-administration and discrimination studies, and human abuse potential studies since the 1960s provide a substantial basis for the present preliminary evaluation. In contrast to Schedule III drugs and even to many drugs placed in Schedule IV, the reinforcing effects in preclinical studies are marginal. There is no clear evidence of physical dependence and withdrawal in preclinical or clinical studies, or among those who chronically used illicit products. Euphoriant effects can occur under limited circumstances but appear attenuated by dysphoric effects. The doses that pose a risk of acute poisoning death (“overdose”) appear to be approximately 1000 times the likely highest clinical dose to be marketed, psychological dependence resulting in daily use appears rare, and all major drug surveillance systems reviewed in Factors 4, 5, and 6 of this analysis indicate rates of abuse, emergency department reports, and treatment seeking in youth and adults that are substantially lower than are evident for many Schedule IV drugs. It is possible, of course that subsequent study with larger populations and different designs in animals and humans, would yield different outcomes, but this review suggests that psilocybin would be appropriately placed in Schedule IV of the CSA if the FDA approves a psilocybin NDA.

The authors of this review recognize that opinions in the general population may differ substantially as it is clear that there remains a legacy of fear regarding psychedelics since the 1960s. The role of the 8-factor analysis of the CSA is to bring science to bear to support the foundation for scheduling, implications for other aspects of scheduling which are based on much of the same data. In particular, this means the labeling that will be specific to the label section, Drug Abuse and Dependence (section 9 of the drug labeling), and warnings including the possible requirement of a Boxed Warning (U.S. Food and Drug Administration, 2017d). As with all approved drug products, determination of safe and effective by FDA does not mean without risk, and the conclusion that the science does not support scheduling more restrictive than IV does not mean no abuse or dependence risk.

3.2 Implications for research and policy

This analysis has implications for future research with psilocybin and for the possible development of related drugs. Perhaps most challenging and important is research to better understand the mechanisms of action of psilocybin and related drugs that can produce profound and very long lasting positive changes in mood and well-being in people who were resistant to standard care and approved medicines. Given the extent to which undertreated and treatment resistant mental and behavioral disorders, including mood, anxiety, and substance use disorders, remain serious problems at the personal and societal levels in the US and globally (Belouin and Henningfield, 2018), it could be concluded that the need for such research is urgent.

The dearth of therapeutic and mechanistic studies of psilocybin and other classic psychedelics over the past half-century does not stem from a lack of interest among psychologists, psychiatrists, pharmacologists and neuroscientists. Research has been and continues to be limited by the provisions of the CSA and the lack of prioritization of such research by potential federal funding agencies. As discussed elsewhere, the barriers to research imposed by Schedule I regulation are formidable and although they do not outright ban such research, the consequence has been that this area of science and potential clinical application has been greatly under-researched (Belouin and Henningfield, 2018; Nutt, 2015; Nutt et al., 2013; Scientific American Editors, 2014; Sinha, 2001; Spillane, 2004; Woodworth, 2011). Several of the key clinical studies have been primarily supported by private foundations rather than federal institutions such as NIH (Bogenschutz et al., 2015; Griffiths et al., 2016; Johnson et al., 2014; Ross et al., 2016).

The science of drug abuse potential assessment has evolved considerably in recent decades and this is evident in the FDA's 2017 guidance document, "Assessment of Abuse Potential of Drugs," that summarizes research strategies, and methods and discusses how these can be brought to bear to provide the regulatory science foundation for drug scheduling decisions. The application of this scientific approach to further evaluate the abuse potential of psilocybin provides an example of how this area of regulatory science has the potential to facilitate innovative therapeutic breakthroughs by replacing fear and misinformation with scientifically based conclusions and facts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Psilocybin mushrooms have been used for millennia for spiritual and medical purposes
- Animal and human studies indicate low abuse and no physical dependence potential
- Major national surveys indicate low rates of abuse, treatment-seeking and harm
- Psilocybin may provide therapeutic benefits supporting its development as a new drug
- Analysis supports the scheduling of psilocybin no more restrictively than Schedule IV

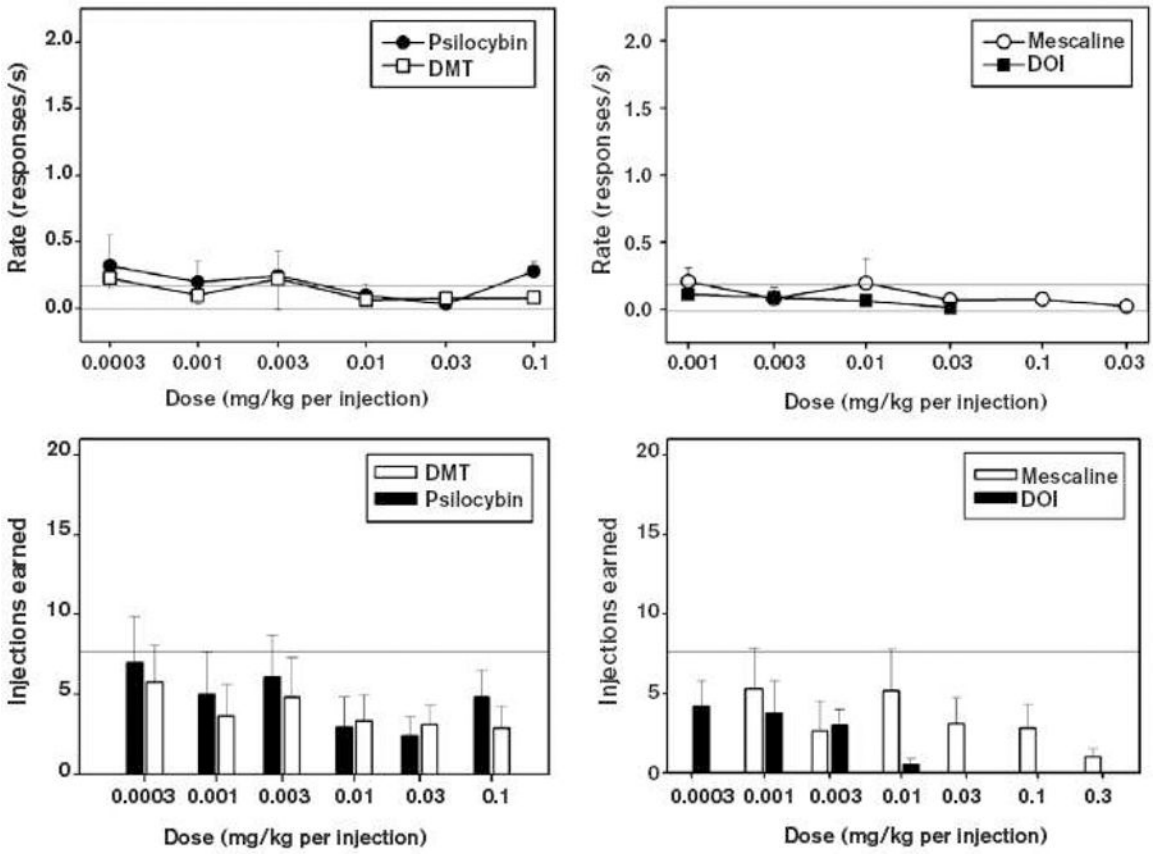

Figure 1:

The two upper panels show mean response rates (±SEM) during self-administration of classic psychedelic compounds by rhesus monkeys making lever presses under an FR-30 schedule of reinforcement. Left panel shows psilocybin and DMT; right panel shows mescaline and 4-iodo-2,5-dimethoxyphenylisopropylamine (DOI). The two bottom panels show the corresponding mean number of injections earned (±SEM) during these self-administration sessions. For all panels, the light horizontal lines show the range for saline response rates (upper panels) and saline injections earned (bottom panels; with the bottom of the range at 0). For all panels, n=4. Figure from Fantegrossi et al, 2004, Figure 1)

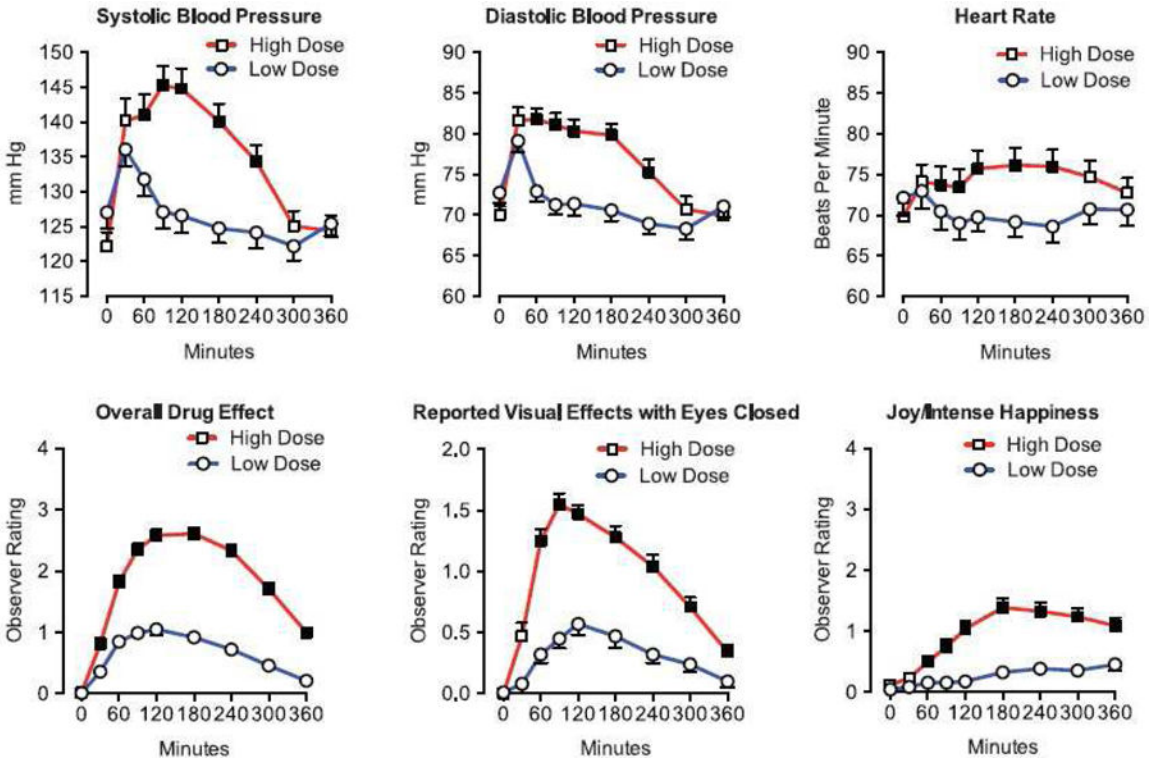

Figure 2:

Cardiovascular and observer-rated effects of oral psilocybin in cancer patients (n=50). Each panel shows the mean (±SEM) within-subject time-course effect of a moderately-high (˜0.314 or ˜0.429 mg/kg) versus low, placebo-like (˜0.014 or ˜0.043 mg/kg) dose of psilocybin. For observer ratings, the Y-axis spans the range of possible scores. Filled squares indicate that planned comparisons showed the high dose condition significantly differed from the low dose condition at that time-point ($p<0.05$). Figure from Griffiths et al, 2016, Figure 2)

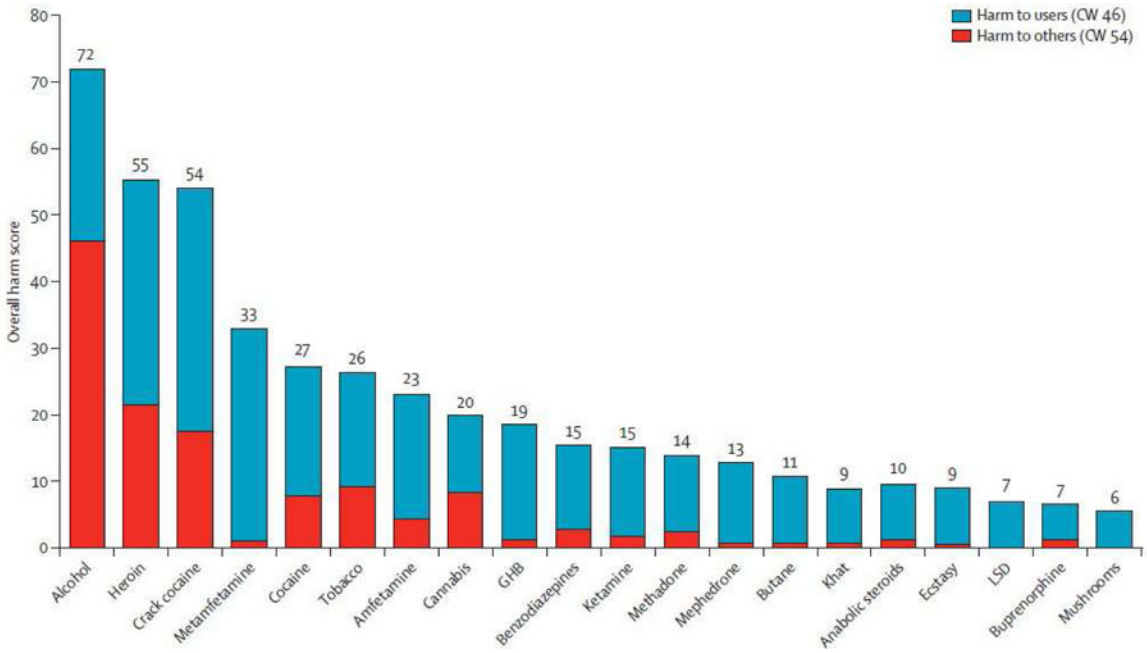

Figure 3:

Normalized ratings of harm potential of psilocybin (“mushrooms”) relative to other drugs as rated by experts in the United Kingdom using on a multidimensional scale. Drugs are ranked by overall harm from left (most harmful) to right (least harmful), with harm to users (blue) and harm to others (red) shown separately. Abbreviations: CW=cumulative weight, GHB=gamma-hydroxybutyric acid. (Figure from Nutt et al., 2010, Figure 2)

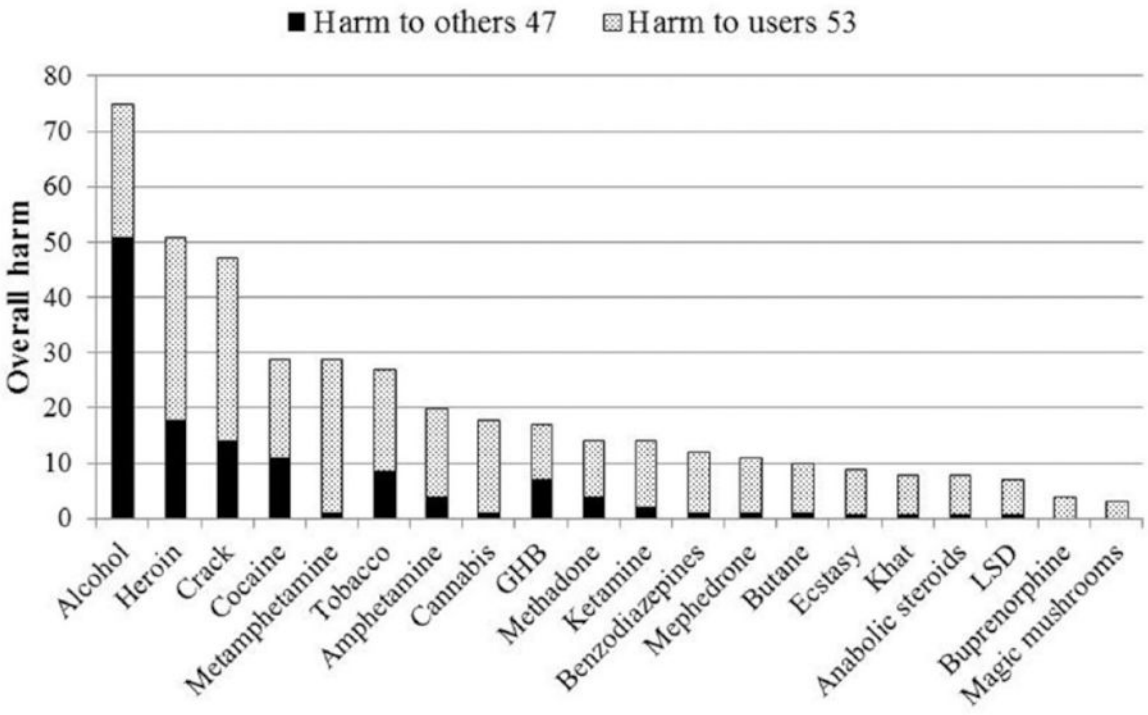

Figure 4:

Normalized ratings of harm potential of psilocybin (“magic mushrooms”) relative to other drugs as rated by experts in the European Union using a multidimensional scale. Drugs are ranked by overall harm from left (most harmful) to right (least harmful), with harm to users (shaded texture) and harm to others (solid texture) shown separately. (Figure 2 from van Amsterdam et al., 2015)

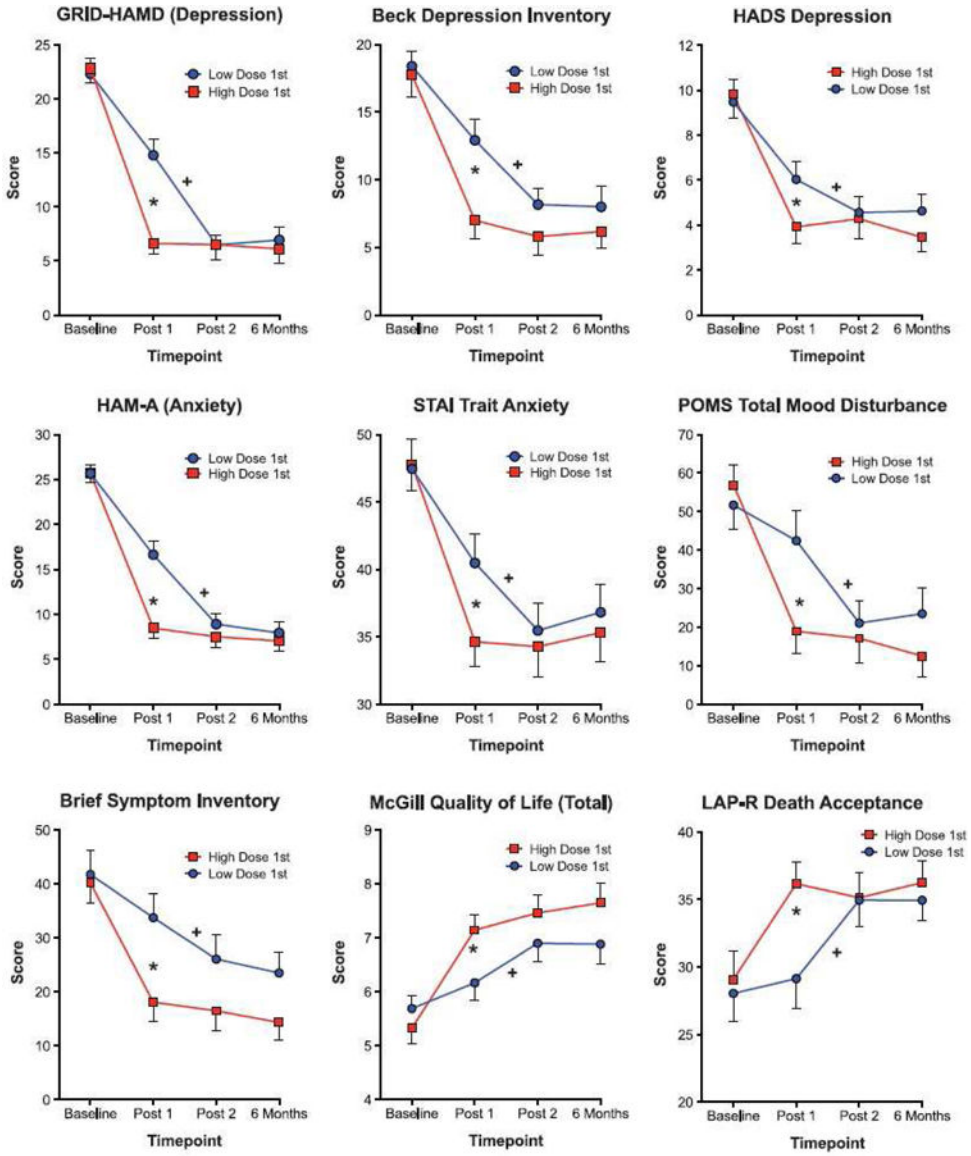

Figure 5:

Persisting effects of psilocybin on depression- and anxiety-related outcome measures Outcomes were measured at baseline (pre-psilocybin), post session 1 (5 weeks after the first psilocybin session), post session 2 (5 weeks after the second psilocybin session), and the 6-month follow-up (n = 25, 25, 24, and 22 at baseline, post session 1, post session 2, and 6 months, respectively). Each panel shows the mean (±SEM) scores for two groups: The "Low Dose 1st" group received a low, placebo-like (˜0.014 or ˜0.043 mg/kg) dose of psilocybin in Session 1, and a moderately-high (˜0.314 or ˜0.429 mg/kg) dose of psilocybin in Session 2; the "High Dose 1st" group received the doses in the opposite order. Stars show a significant difference between the two groups at post session 1 by planned comparison ($p<0.05$). Crosses show a significant difference between the post session 1 and post session 2 times in the Low-Dose-1st group by planned comparison ($p<0.05$). (Figure from Griffiths et al., 2016, Figure 3)

Table 1.

The Addiction Research Center Inventory

Through the 1950s the term for assessing potential addictive and abuse-related drug effects was "addiction liability" assessment and the major focus of assessment was on the development of tolerance and the emergence of withdrawal signs and symptoms upon discontinuation of drug administration (Himmelsbach and Andrews, 1943). In the late 1950s Isbell, Frazier and colleagues at the ARC came to conclude that the mood and behavior altering effects of drugs contributed to and were predictive of the risk of abuse and addiction and that these could be evaluated by psychometric instruments. The simplest and most commonly relied upon measure in human abuse potential studies to support new drug applications to the FDA is the drug liking scale that was originally a five-point scale in which subjects rated their liking of the drug from 0 (not at all) to 4 (an awful lot). This scale development benefitted from the then recent observations of Beecher (Beecher, 1952, 1957) who demonstrated that such scales could be used to reliably assess pain and analgesia (Beecher, 1952, 1957; Lasagna et al., 1955). Such positive mood alterations could be produced by drugs of abuse that were not then known to produce physical dependence and withdrawal, and by single doses of opioids in former opioid users (referred to as "post-addicts") who were no longer physically dependent (Jasinski, 1977; Jasinski and Henningfield, 1989; Jasinski et al., 1984; U.S. Food and Drug Administration, 2017a).

As predominant theories of addiction at the time included the potential importance of personality disorders, a psychologist who was expert in the Minnesota Multiphasic Personality Inventory and testing, Charles Haertzen, was hired in 1959, to take the lead in developing a comprehensive instrument to better characterize and differentiate the several categories of substances that were abused as well as the personality characteristics of those who used them. The resulting Addiction Research Center Inventory (ARCI) contained more than 500 true and false items, but shorter versions containing 40 or 49 items were most commonly used in human abuse potential studies. The ARCI scale that provided the most robust indicator of high abuse potential was the Morphine Benzedrine Group (MBG) scale, commonly referred to as the "euphoria" scale because it was empirically derived based on the response of volunteers to the prototypic euphoriants morphine and Benzedrine® (hence, the MBG scale) which produced robustly elevated mood and feeling states. In contrast, a scale based on responses to LSD (LSD scale) was distinguished by a cluster of items, that included unpleasant, dysphoric, or psychotomimetic responses to LSD (hence the LSD scale) that were associated with a lower propensity to compulsively or frequently self-administer the substance; it was often referred to as the "dysphoria" scale (Haertzen and Hill, 1963; Jasinski et al., 1984). It also included scales based on clusters of items that were associated with amphetamine administration (the A scale) and one that reflected the somewhat overlapping and sedating effects of pentobarbital, chlorpromazine, and atropine group of drugs (the PCAG scale). Most drugs of high abuse potential produced elevations in the scores on the MBG scale as well as on the specific scale that reflected their pharmacological class. Thus, alcohol, barbiturates, opioids, and stimulants could all increase MBG scale robustly as well as the scale that was specific to their class. Chlorpromazine and atropine, by contrast, which were rarely abused, did not reliably elevate MBG scale scores but might elevate LSD scale scores. LSD elevated LSD scale scores and sometimes elevated MBG scale scores and liking scores, reflecting their overall low abuse potential and diverse effects that can range from fear and anxiety to pleasure, depending much on dose, time since drug, experience, and other factors (Griffiths et al., 2008).

Examples of a few of the items that distinguished drugs likely to elevate scores on the MBG scale as compared to items characterizing the LSD scale are the following: "I would be happy all the time if I felt as I do now" - scored positively on the MBG scale and negatively on the LSD scale; "I am in the mood to talk about the feeling I have" and "I feel more clear-headed than dreamy" - were both score positively on the MBG scale and were not included on the LSD scale. The LSD scale also contained numerous items reflective of mixed mood effects, e.g., "I feel anxious and upset" and "I have a weird feeling" – both scored positively; negatively scored items included "I feel very patient", and "My movements are free, relaxed and pleasurable"; and, items reflective of introspection and negative feelings included "I have a negative disturbance in my stomach", "Some parts of my body are tingling", and "It seems I'm spending longer than I should on each of these questions" (Haertzen and Hickey, 1987; Jasinski and Henningfield, 1989).

Over more than 50 years of research, it became clear that drugs with the highest overall abuse potential were those that produced robust increases in scores on drug liking scale and the MBG scale, and low effects on the LSD scale (Griffiths et al., 1980; Griffiths and Balster, 1979; Haertzen and Hickey, 1987; Jasinski and Henningfield, 1989; Jasinski et al., 1984). Liking scales have since evolved into the more commonly used 100-point (or 100mm) visual line analog scales and the ARCI often replaced with scales to assess positive (pleasant) and negative (unpleasant) effects as described in early 2000 expert reviews and advised by FDA in its abuse potential assessment guidance (Carter and Griffiths, 2009; Griffiths et al., 2003; U.S. Food and Drug Administration, 2017a).

The ARCI helped elucidate a major difference in nature and magnitude of the abuse potential that is associated with psychedelics, as compared to substances that carry a high risk of compulsive patterns of repetitive use and abuse including amphetamine, cocaine, the cigarette form of nicotine delivery, prototypic opioids, and sedatives, as compared to substances with substantially lower potential for compulsive use and abuse, such as LSD and psilocybin (see also Table 1).

Table 2

History of psilocybin use and in culture

7000 BCE-5000 BCE – Mushroom cave paintings from Tassilli, modern-day Algeria (Samorini, 1992)
4000 BCE – Possible evidence of psilocybin-containing mushroom use in cave paintings in modern-day Spain (Akers et al., 2011)
4000 BCE-900 CE – Mushroom stones and other artifacts from cultures throughout the Americas, including Mayan (de Borhegyi, 1961; Lowy, 1971; Schultes, 1969; Schultes et al., 2001; Truttman, 2012)
1600 – Spanish colonizers documented religious mushroom use by indigenous people in Mexico, considered it devil worship, and persecuted its use. Sacramental use was driven underground for the next 400 years (Schultes, 1969; Schultes et al., 2001).
1957 – Spanish conqueror accounts of mushroom use had come to be considered myth (Schultes, 1969). Then, following earlier suggestive evidence by R. Schultes (Schultes, 1939, 1940), R.G. Wasson became the first non-indigenous individual to participate in and document sacramental psilocybin-containing mushroom use by indigenous people (Mazatec society in Mexico) since European colonization (Wasson, 1959; Wasson and Wasson, 1957)
1958–1959 – A. Hofmann, using mushrooms provided by R.G. Wasson, isolated psilocybin and psilocin, then developed synthesis of each (Hofmann, 1958; Hofmann et al., 1958; Hofmann et al., 1959)
1959 – Clinical research was begun; initial research did not appreciate the powerful influences of set and setting, resulting in erratic outcomes (Delay et al., 1959)
1960s – Societal, legal, and political backlash emerged against the psychoactive drug excesses of the 1960s, along with the associated “counter-culture”, the promotion of psychedelics as a panacea for achieving personal enlightenment and a utopian transformation of society, as opposed to use primarily as potential medicines in people with illness
Early 1960s – Indocybin marketing for research by Sandoz requiring therapeutic interventions, ending in 1966
1970 – US Controlled Substances Act listed psilocybin in Schedule I, along with LSD, heroin and other substances of serious societal and public health concern, thus prohibiting therapeutic use, and imposing extensive barriers to possession and research
1971–1990s – Human psilocybin research was largely dormant until the late 1990s when a few laboratories in Europe renewed interest (Spitzer et al., 1996; Vollenweider et al., 1997). Human psilocybin research then began in the U.S. at the University of New Mexico (Bogenschutz et al., 2015; Strassman, 2001) [initiated but unpublished psilocybin results], Johns Hopkins University (Griffiths et al , 2006), the University of Arizona (Moreno et al , 2006), the University of California, Los Angeles (Grob et al., 2011), and New York University (Ross et al., 2016).

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Table 3

Treatment Episode Datasets (TEDS): Rate of Various Drugs as the Primary Substance of Abuse Among Persons 12 Years and Older, 2005–2015

Primary Substance	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total	1,896,299	1,962,664	1,969,862	2,074,974	2,055,914	1,932,524	1,936,278	1,834,591	1,762,015	1,639,125	1,537,025
Hallucinogens											
n	2,045	1,644	1,651	1,917	1,880	1,791	1,998	2,155	2,177	1,899	1,917
%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Opiates											
n	332,401	353,899	364,614	411,301	439,826	443,405	486,729	488,038	507,989	501,680	526,686
%	17.5%	18.0%	18.5%	19.8%	21.4%	22.9%	25.1%	26.6%	28.8%	30.6%	34.3%
Cocaine											
n	268,402	277,852	259,973	239,342	193,419	158,780	152,349	126,371	106,594	88,623	74,710
%	14.2%	14.2%	13.2%	11.5%	9.4%	8.2%	7.9%	6.9%	6.0%	5.4%	4.9%
Alcohol*											
n	746,544	781,349	804,581	860,742	856,180	782,764	759,017	709,891	654,808	591,404	521,089
%	39.4%	39.8%	40.8%	41.5%	41.6%	40.5%	39.2%	38.7%	37.2%	36.1%	33.9%

*Alcohol only or with a secondary drug

Source: (Substance Abuse and Mental Health Services Administration, 2017a)

Table 4

Drug Abuse Warning Network (DAWN): Total ED Visits (Any Type) for Various Drugs, 2004–2011

Drugs	2004	2005	2006	2007	2008	2009	2010	2011
Total ED visits	2,537,722	3,009,025	3,441,855	3,998,228	4,383,494	4,595,261	4,916,328	5,067,374
Psilocybin								
number of ED visits	2,947	2,937	3,557	4,006	5,422	4,087	4,539	6,048
% of all ED visits	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Rate per 100,000 population	1.0	1.0	1.2	1.3	1.8	1.3	1.5	1.9
Opiates/opioids								
number of ED visits	299,498	388,873	452,929	542,699	668,803	769,330	851,453	855,348
% of all ED visits	11.8%	12.9%	13.2%	13.6%	15.3%	16.7%	17.3%	16.9%
Rate per 100,000 population	102.3	131.6	151.8	180.2	219.9	250.8	275.3	274.5
Cocaine								
number of ED visits	475,425	483,865	548,608	553,535	482,188	422,902	488,101	505,224
% of all ED visits	18.7%	16.1%	15.9%	13.8%	11.0%	9.2%	9.9%	10.0%
Rate per 100,000 population	162.4	163.7	183.9	183.8	158.6	137.9	157.8	162.1
Alcohol								
number of ED visits	674,914	527,198	577,525	634,663	656,911	658,263	687,574	724,306
% of all ED visits	26.6%	17.5%	16.8%	15.9%	15.0%	14.3%	14.0%	14.3%
Rate per 100,000 population	230.5	178.4	193.6	210.7	216.0	214.6	222.3	232.5

Source: (Substance Abuse and Mental Health Services Administration, 2013)

Table 5

National Survey on Drug Use and Health (NSDUH): Lifetime Use of Various Drugs Among Persons Aged 12 and Older, 2009–2015

	2009	2010	2011	2012	2013	2014	2015
Psilocybin							
% lifetime	8.4%	8.3%	8.1%	8.1%	8.7%	8.5%	8.5%
% past year	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Pain Relievers							
% lifetime	14.0%	13.8%	13.3%	14.2%	13.5%	13.6%	10.3%*
% past year	4.9%	4.8%	4.3%	4.8%	4.2%	3.9%	4.7%*
Cocaine							
% lifetime	14.6%	14.7%	14.3%	14.5%	14.3%	14.8%	14.5%
% past year	1.9%	1.8%	1.5%	1.8%	1.6%	1.7%	1.8%
Alcohol							
% lifetime	82.8%	82.5%	82.2%	82.3%	81.5%	82.1%	81.0%
% past year	66.8%	66.4%	66.2%	66.7%	66.3%	66.6%	65.7%

* NSDUH metric was “non-medical use” from 2009–2014, but changed to “misuse” in 2015. Additionally, the focus of the survey shifted from lifetime to past-year (for most drugs) in 2015. SAMHSA has suggested that these methods changes may cause trend breaks for some drugs, including pain relievers. Thus, caution needs to be applied when comparing 2015 estimates to those from 2009–2014.

N/A = not assessed

Source: (Substance Abuse and Mental Health Services Administration, 2017b)

Table 6

National Forensic Laboratory Information System (NFLIS): Estimated percentage of total drug reports submitted to laboratories for various drugs, 2010–2015

Drug	2010	2011	2012	2013	2014	2015
Psilocin/Psilocybin	0.30%	0.31%	0.31%	0.27%	0 26%	0.26%
Cocaine	21.44%	20.10%	16.54%	15.63%	14.10%	13.95%
Heroin	6.44%	7.21%	8.11%	9.85%	10.83%	12.12%
Oxycodone	3.56%	3.61%	3.40%	2.96%	2.85%	2.70%
Hydrocodone	2.81%	2.82%	2.66%	2.41%	2 19%	1.76%
Buprenorphine	0.61%	0.66%	0.73%	0.78%	1.01%	1.16%
MDMA	1.48%	0.78%	0.37%	0.31%	0 32%	5.188

Sources: (Drug Enforcement Administration Diversion Control Division, 2011, 2012, 2013, 2014, 2015, 2016)

Table 7

American Association of Poison Control Centers' (AAPCC) National Poison Data System (NPDS), 2007–2015

Drug		2007	2008	2009	2010	2011	2012	2013	2014	2015
Mushrooms: Hallucinogenics (Psilocybin and Psilocin)										
	# of Case Mentions	773	758	727	643	633	593	476	484	473
	# of Single Exposures	609	574	565	478	462	409	342	335	311
	Unintentional	83	82	59	74	40	44	50	49	32
	Intentional	511	479	495	394	408	350	285	266	266
	No Outcome	40	37	33	23	27	24	38	23	18
	Minor Outcome	112	92	111	92	104	69	64	83	75
	Moderate Outcome	257	248	243	193	187	180	142	142	137
	Major Outcome	9	9	11	6	4	8	5	7	5
	Death	0	0	0	0	0	1	0	0	0
Cocaine										
	# of Case Mentions	7634	6351	5293	5130	5485	4850	4749	4289	4738
	# of Single Exposures	2748	2075	1707	1582	1597	1345	1265	1171	1160
	Unintentional	281	261	184	162	168	140	133	105	127
	Intentional	2323	1695	1448	1329	1327	1133	1041	974	933
	No Outcome	488	419	349	234	231	191	197	175	195
	Minor Outcome	301	281	264	248	245	219	213	195	189
	Moderate Outcome	649	474	431	426	435	372	313	343	320
	Major Outcome	140	121	88	90	101	70	77	60	65
	Death	20	18	6	10	34	28	20	9	7
Codeine										
	# of Case Mentions	974	965	2056	1993	2054	1953	1935	1709	1824
	# of Single Exposures	629	616	1550	1501	1542	1467	1395	1254	1327
	Unintentional	499	449	1307	1270	1280	1215	1164	1049	1073
	Intentional	90	109	163	152	186	163	160	133	185

Drug		2007	2008	2009	2010	2011	2012	2013	2014	2015
	No Outcome	158	123	413	409	403	389	364	345	332
	Minor Outcome	84	71	176	155	192	177	166	148	182
	Moderate Outcome	13	17	27	31	26	33	28	29	30
	Major Outcome	1	1	5	1	3	1	2	5	3
Hydrocodone Alone or in Combination[a, b]										
	# of Case Mentions	-	-	-	316	1986	1989	1943	1956	1853
	# of Single Exposures	-	-	-	193	1089	1065	974	989	862
	Unintentional	-	-	-	116	675	698	604	646	538
	Intentional	-	-	-	59	297	247	271	243	234
	No Outcome	-	-	-	26	190	203	157	188	163
	Minor Outcome	-	-	-	47	246	215	188	211	161
	Moderate Outcome	-	-	-	14	67	51	63	47	46
	Major Outcome	-	-	-	0	10	3	2	2	2
	Death	-	-	-	0	1	0	0	4	1
Oxycodone Alone or in Combination[c]										
	# of Case Mentions	6515	7692	8065	9157	8963	8460	7742	7740	8170
	# of Single Exposures	3340	3741	3803	4278	3973	3644	3363	3300	3506
	Unintentional	1667	1980	1945	2102	1886	1820	1806	1763	1912
	Intentional	1271	1415	1463	1746	1700	1449	1231	1286	1319
	No Outcome	488	700	621	700	659	657	656	649	745
	Minor Outcome	560	615	714	804	758	673	655	782	775
	Moderate Outcome	260	289	368	478	469	409	387	397	431
	Major Outcome	78	85	91	112	108	105	90	81	109
	Death	9	11	8	12	37	26	20	15	13
Alcohol (Ethanol Beverages)										
	# of Case Mentions	47202	50919	51909	51549	53021	54445	50763	49305	51811

Drug		2007	2008	2009	2010	2011	2012	2013	2014	2015
	# of Single Exposures	8668	8560	9937	9307	9166	9753	7954	6026	6761
	Unintentional	2428	2496	2640	2381	2371	2363	2218	2076	2190
	Intentional	5668	5512	6729	6223	6169	6738	5099	3340	3947
	No Outcome	1010	1153	1124	894	880	694	706	662	704
	Minor Outcome	1280	1174	1570	1498	1446	1567	1220	984	1237
	Moderate Outcome	915	935	1074	1099	1062	1221	1162	1021	1127
	Major Outcome	185	185	202	225	208	220	234	219	260
	Death	5	20	8	21	71	111	79	15	20

[a] Excluding Combination Products with Acetaminophen, Acetylsalicylic Acid or Ibuprofen

[b] NFLIS started reporting Hydrocodone alone or in combination in 2010

[c] Excluding Combination Products with Acetaminophen or Acetylsalicylic Acid

Sources: (Bronstein et al., 2011; Bronstein et al., 2009, 2010; Bronstein et al., 2008; Bronstein et al , 2012; Mowry et al , 2015;Mowry et al., 2016; Mowry et al., 2013; Mowry et al., 2014)

JAMA Psychiatry | Original Investigation

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder
A Randomized Clinical Trial

Alan K. Davis, PhD; Frederick S. Barrett, PhD; Darrick G. May, MD; Mary P. Cosimano, MSW; Nathan D. Sepeda, BS; Matthew W. Johnson, PhD; Patrick H. Finan, PhD; Roland R. Griffiths, PhD

IMPORTANCE Major depressive disorder (MDD) is a substantial public health burden, but current treatments have limited effectiveness and adherence. Recent evidence suggests that 1 or 2 administrations of psilocybin with psychological support produces antidepressant effects in patients with cancer and in those with treatment-resistant depression.

OBJECTIVE To investigate the effect of psilocybin therapy in patients with MDD.

DESIGN, SETTING, AND PARTICIPANTS This randomized, waiting list–controlled clinical trial was conducted at the Center for Psychedelic and Consciousness Research at Johns Hopkins Bayview Medical Center in Baltimore, Maryland. Adults aged 21 to 75 years with an MDD diagnosis, not currently using antidepressant medications, and without histories of psychotic disorder, serious suicide attempt, or hospitalization were eligible to participate. Enrollment occurred between August 2017 and April 2019, and the 4-week primary outcome assessments were completed in July 2019. A total of 27 participants were randomized to an immediate treatment condition group (n = 15) or delayed treatment condition group (waiting list control condition; n = 12). Data analysis was conducted from July 1, 2019, to July 31, 2020, and included participants who completed the intervention (evaluable population).

INTERVENTIONS Two psilocybin sessions (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg) were given (administered in opaque gelatin capsules with approximately 100 mL of water) in the context of supportive psychotherapy (approximately 11 hours). Participants were randomized to begin treatment immediately or after an 8-week delay.

MAIN OUTCOMES AND MEASURES The primary outcome, depression severity was assessed with the GRID-Hamilton Depression Rating Scale (GRID-HAMD) scores at baseline (score of ≥17 required for enrollment) and weeks 5 and 8 after enrollment for the delayed treatment group, which corresponded to weeks 1 and 4 after the intervention for the immediate treatment group. Secondary outcomes included the Quick Inventory of Depressive Symptomatology-Self Rated (QIDS-SR).

RESULTS Of the randomized participants, 24 of 27 (89%) completed the intervention and the week 1 and week 4 postsession assessments. This population had a mean (SD) age of 39.8 (12.2) years, was composed of 16 women (67%), and had a mean (SD) baseline GRID-HAMD score of 22.8 (3.9). The mean (SD) GRID-HAMD scores at weeks 1 and 4 (8.0 [7.1] and 8.5 [5.7]) in the immediate treatment group were statistically significantly lower than the scores at the comparable time points of weeks 5 and 8 (23.8 [5.4] and 23.5 [6.0]) in the delayed treatment group. The effect sizes were large at week 5 (Cohen *d* = 2.5; 95% CI, 1.4-3.5; *P* < .001) and week 8 (Cohen *d* = 2.6; 95% CI, 1.5-3.7; *P* < .001). The QIDS-SR documented a rapid decrease in mean (SD) depression score from baseline to day 1 after session 1 (16.7 [3.5] vs 6.3 [4.4]; Cohen *d* = 2.6; 95% CI, 1.8-3.5; *P* < .001), which remained statistically significantly reduced through the week 4 follow-up (6.0 [5.7]; Cohen *d* = 2.3; 95% CI, 1.5-3.0; *P* < .001). In the overall sample, 17 participants (71%) at week 1 and 17 (71%) at week 4 had a clinically significant response to the intervention (≥50% reduction in GRID-HAMD score), and 14 participants (58%) at week 1 and 13 participants (54%) at week 4 were in remission (≤7 GRID-HAMD score).

CONCLUSIONS AND RELEVANCE Findings suggest that psilocybin with therapy is efficacious in treating MDD, thus extending the results of previous studies of this intervention in patients with cancer and depression and of a nonrandomized study in patients with treatment-resistant depression.

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Major depressive disorder (MDD) is a substantial public health concern, affecting more than 300 million individuals worldwide. Depression is the number one cause of disability,[1] and the relative risk of all-cause mortality for those with depression is 1.7 times greater than the risk for the general public.[2] In the United States, approximately 10% of the adult population has been diagnosed with MDD in the past 12 months,[3] and the yearly economic burden of MDD is estimated to be $210 billion.[4]

Although effective pharmacotherapies for depression are available, these drugs have limited efficacy, produce adverse effects, and are associated with patient adherence problems.[5] Although many patients with depression showed reduced or remitted symptoms after treatment with existing pharmacotherapies,[6] approximately 30% to 50% of patients did not respond fully and as many as 10% to 30% of patients were considered treatment-resistant, resulting in average effects that were only modestly larger than the effects of placebo.[7,8]

Most of the current pharmacotherapies for MDD, including the widely used selective serotonin reuptake inhibitors, increase levels of brain monoamine neurotransmitters such as serotonin and norepinephrine (typically by blocking reuptake).[6] A growing body of evidence suggests that newer ketamine-like medications exert therapeutic efficacy in MDD through effects on glutamate neurotransmission.[9,10] Ketamine hydrochloride, a nonselective *N*-methyl-D-aspartate receptor antagonist, is the most well-researched of these newer medications. Several studies have demonstrated the efficacy of a single ketamine infusion in rapidly (within hours) reducing depression symptoms and, when effective, lasting from a few days to about 2 weeks.[10,11] However, ketamine has high abuse liability, and its administration involves moderate physiological risk that requires medical monitoring.[12]

The combined serotonergic and glutamatergic action of psilocybin[13-15] (a classic hallucinogen) and the preliminary evidence of the antidepressant effects of psilocybin-assisted therapy (among patients with life-threatening cancer or patients with treatment-resistant depression)[16-18] indicate the potential of psilocybin-assisted therapy as a novel antidepressant intervention.[19] Moreover, psilocybin has lower addiction liability and toxic effects compared with ketamine[20-22] and is generally not associated with long-term perceptual, cognitive, or neurological dysfunction.[23]

The substantial negative public health impact of MDD underscores the importance of conducting more research into drugs with rapid and sustained antidepressant effects. Current pharmacotherapies for depression have variable efficacy and unwanted adverse effects. Novel antidepressants with rapid and sustained effects on mood and cognition could represent a breakthrough in the treatment of depression and may potentially improve or save lives. Therefore, the primary objective of this randomized clinical trial was to investigate the effect of psilocybin therapy in patients with MDD.

Key Points

Question Is psilocybin-assisted therapy efficacious among patients with major depressive disorder?

Findings In this randomized clinical trial of 24 participants with major depressive disorder, participants who received immediate psilocybin-assisted therapy compared with delayed treatment showed improvement in blinded clinician rater–assessed depression severity and in self-reported secondary outcomes through the 1-month follow-up.

Meaning This randomized clinical trial found that psilocybin-assisted therapy was efficacious in producing large, rapid, and sustained antidepressant effects in patients with major depressive disorder.

Method

This randomized, waiting list–controlled clinical trial was conducted at the Center for Psychedelic and Consciousness Research in Baltimore, Maryland. The Johns Hopkins Medicine Institutional Review Board approved this trial (the protocol is included in Supplement 1). Written informed consent was obtained from all participants.

Study Design and Participants

This trial of psilocybin therapy included participants with moderate or severe MDD episodes, as assessed with the Structured Clinical Interview for DSM-5 (SCID-5)[24] and the GRID-Hamilton Depression Rating Scale (GRID-HAMD; a score of ≥17 was required for enrollment).[25,26] Eligible candidates were aged 21 to 75 years who self-reported no current pharmacotherapy for depression at trial screening. To avoid the confounding effects and potential interactions of concurrent antidepressant use, candidates were required to refrain from using antidepressants (eg, selective serotonin reuptake inhibitors) for at least 5 half-lives before the screening and up to 4 months after enrollment (through the completion of the primary outcome assessment). However, the decision to taper off and/or continuing not to take their medications during the study was made by the individuals and their prescribing physicians and not by study personnel. Additional eligibility requirements included being medically stable with no uncontrolled cardiovascular conditions; having no personal or family history (first or second degree) of psychotic or bipolar disorders; and, for women, being nonpregnant, being non-nursing, and agreeing to use contraception. Individuals with a moderate or severe alcohol or other drug use disorder (including nicotine) in the past year, as defined by *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*) criteria, were excluded, as were individuals with substantial lifetime use (>10 total) or recent use (past 6 months) of ketamine or classic hallucinogens, such as psilocybin-containing mushrooms or lysergic acid diethylamide (eMethods in Supplement 2).

Participants were enrolled between August 2017 and April 2019, and the 4-week primary outcome assessments were completed in July 2019. Recruitment was carried out through flyers, print advertisements, internet forums, social media, and

the study website. Of the 870 individuals screened by telephone or electronic screening survey, 70 went on to undergo in-person medical and psychological screening, 43 were disqualified, and 27 qualified and were enrolled in the study. After screening, baseline assessments, and enrollment, 27 participants were randomized to either the immediate treatment group or the delayed treatment group (ie, the waiting list control condition). The use of a delayed treatment control was chosen to differentiate the psilocybin intervention from spontaneous symptom improvement. The delay interval was 8 weeks, after which participants in the delayed treatment group underwent all study assessments and entered the study intervention period. Randomization to the immediate treatment and delayed treatment groups occurred after screening and baseline assessments (**Figure 1**). Participants were randomized using urn randomization,[27] balancing for sex, age, depression severity at screening (assessed using the GRID-HAMD), and level of treatment resistance (assessed using the Maudsley Staging Method).[28] One of us (F.S.B.), who was not involved in participant screening or enrollment, performed urn randomization using the randPack library, version 1.32.0,[29] in the R Statistical Software package (R Foundation for Statistical Computing).[30]

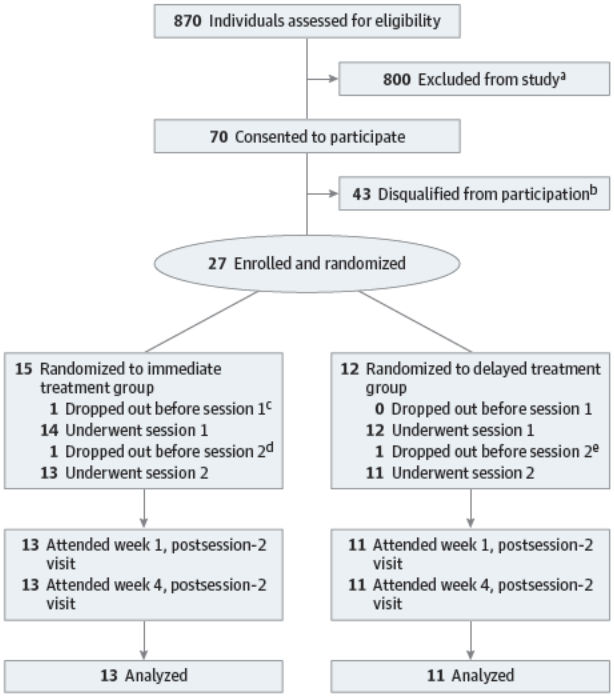
Participants received no monetary compensation for undergoing the intervention. However, participants received a total of $200 for completing 2 magnetic resonance imaging sessions.

Immediate Treatment Condition

The intervention period was 8 weeks and involved at least 18 in-person visits, including 2 daylong psilocybin administration sessions (**Figure 2**). Consistent with previous studies using psilocybin,[16,31] the visit schedule included preparatory meetings (8 hours in total) with 2 session facilitators before the first psilocybin session as well as follow-up meetings after psilocybin sessions (2-3 hours in total) (eMethods in Supplement 2). Session facilitators were study staff with varying educational levels (ie, bachelor's, master's, doctorate, and medical degrees) and professional disciplines (eg, social work, psychology, and psychiatry). After the preparation meetings, 2 psilocybin administration sessions were conducted a mean of 1.6 weeks apart (no statistically significant differences were found between conditions; eResults in Supplement 2). The psilocybin dose was moderately high (20 mg/70 kg) in session 1 and was high (30 mg/70 kg) in session 2. Procedures for psilocybin administration and the conduct of the sessions were similar to procedures used in previous and ongoing studies with psilocybin (eMethods in Supplement 2) at the Center for Psychedelic and Consciousness Research.[16,32,33]

Psilocybin was administered in opaque gelatin capsules with approximately 100 mL water. Both facilitators were present in the room and available to respond to participants' physical and emotional needs during the day-long session, with the exception of short breaks taken by 1 facilitator at a time. During the session, participants were instructed to lie on a couch in a living room–like environment, and facilitators encouraged participants to focus their attention inward and stay with any experience that arose. To enhance inward reflection, music was played (the playlist is provided in the eMethods in Supplement 2), and participants were instructed to wear eyeshades and headphones.

Figure 1. CONSORT Diagram of Participant Flow



[a] After completing the prescreening questionnaire, people were deemed ineligible if they were currently using antidepressant medication (n = 157); lived outside reasonable commuting distance (n = 161); did not meet criteria for the magnetic resonance imaging scans (n = 99); had a first- or second-degree relative with a diagnosis of schizophrenia spectrum, bipolar I or II, or other psychotic disorder (= 77); had a recent history of substance use disorder (n = 50); opted out of in-person screening (n = 38); were not in a current depressive episode (n = 37); were more than 25% beyond the upper or lower range of recommended body weight (n = 32); had a medically significant suicide attempt (n = 30); had lifetime hallucinogen use that exceeded the exclusion threshold (n = 30); if major depressive disorder (MDD) was not primary psychiatric diagnosis (n = 18); if they had a medical exclusion (n = 11); had exclusionary use of nonserotonergic psychoactive medication (n = 11); or failed to respond to electroconvulsive therapy during current depressive episode (n = 4). Forty-five people were ineligible for other reasons.

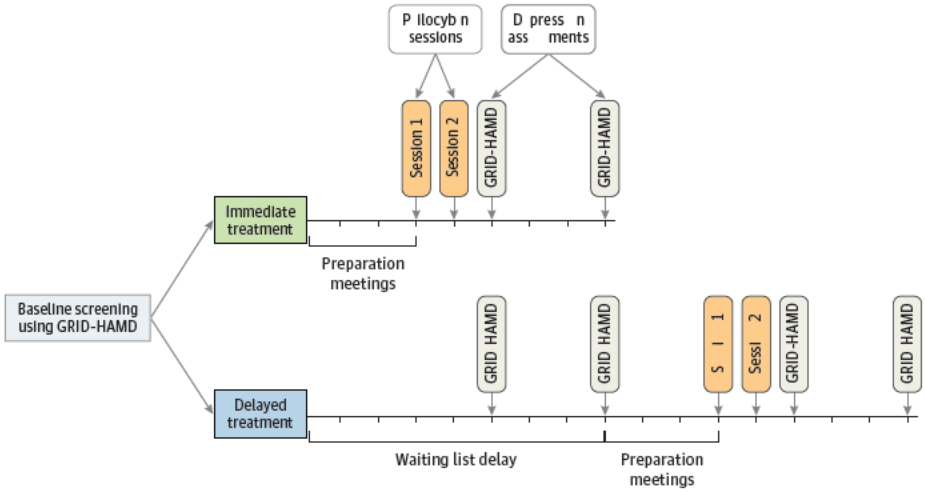
[b] People were deemed ineligible during in-person screening if they had a psychiatric condition judged to be incompatible with establishment of rapport or safe exposure to psilocybin (n = 17); did not have confirmed *DSM-5* diagnosis of MDD (n = 7); had a recent history of moderate to severe substance use disorder (n = 5); were at high risk for suicidality (n = 3); disagreed with study procedures (n = 3); had a baseline GRID Hamilton Depression Rating Scale score lower than the eligibility threshold of 17 (n = 2); had cardiovascular conditions (n = 2); had lifetime hallucinogen use that exceeded the exclusion threshold (n = 2); were currently taking serotonergic medication (n = 1); or were more than 25% beyond the upper and lower range of recommended body weight (n = 1).

[c] Dropped out of the study due to anticipatory anxiety about the upcoming first psilocybin session.

[d] Dropped out of study due to sleep difficulties. Sleep difficulties were also reported at screening, and it was not clear whether sleep difficulties were exacerbated by the intervention.

[e] Participant showed a marked reduction in depression symptoms immediately following the first psilocybin session and chose not to proceed with the intervention.

Figure 2. Study Timeline From Baseline Assessment and Screening to the 4-Week Postsession-2 Follow-up Visit



GRID-HAMD indicates GRID Hamilton Depression Rating Scale.

Delayed Treatment Condition

For safety during the 8-week delay period of the delayed treatment group, participants were monitored weekly by in-person assessment or brief telephone calls. In weeks 5 and 8, participants attended an in-person visit and underwent the GRID-HAMD assessment and other study measures. In other weeks of the delay period, participants received telephone calls that included a brief check-in and assessment for self-reported suicidal ideation or behavior and depression symptoms. All assessments during the delay period were administered by study staff who were not lead facilitators. At the end of the delay period, all participants in the delayed treatment group completed the same intervention as the participants in the immediate treatment group.

Outcome Assessments

Screening evaluation included a preliminary questionnaire administered via telephone or an online survey as well as an in-person medical history and physical examination, electrocardiogram, routine medical blood and urinalysis laboratory tests, and structured assessments (eg, SCID-5, SCID-5 Screening Personality Questionnaire, SCID-5 Personality Disorders, and Personality Assessment Inventory).[24,34-36]

The primary outcome measure was the GRID-HAMD,[37] a version of the 17-item Hamilton Depression Rating Scale that has high reliability and validity.[26] The GRID-HAMD was administered by blinded clinician raters via telephone at baseline and at postrandomization weeks 5 and 8 for participants in the delayed treatment group and at the weeks 1 and 4 follow-up visits after the second psilocybin session for participants in both the immediate treatment and delayed treatment groups. The primary between-group end point comparison was at weeks 5 and 8 between the immediate treatment and delayed treatment groups (Figure 2). The primary within-group end point comparison was between baseline and weeks 1 and 4 postsession 2 follow-up visits in both groups.

Severity of depression was assessed using the total GRID-HAMD score (0-7: no depression; 8-16: mild depression; 17-23: moderate depression; ≥24: severe depression).[38] A clinically significant response was defined as 50% or greater decrease from baseline; symptom remission was defined as a score of 7 or lower. The GRID-HAMD assessment was audiorecorded to examine interrater reliability (eMethods in Supplement 2). Interrater reliability for all depression assessments (through postsession week 4) was 85%. Rapid and sustained antidepressant effects were examined at baseline; at day 1 and week 1 of postsession-1 follow-up; and at day 1, week 1, and week 4 postsession-2 follow-up using the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR; score range: 0-27, with higher scores indicating very severe depression).[39]

Descriptions of secondary outcome measures and timing of assessment are provided in the eMethods in Supplement 2. Secondary outcome measures for depressive symptoms were the Beck Depression Inventory II (score range: 0-63, with higher scores indicating severe depression)[40] and the 9-item Patient Health Questionnaire (score range: 0-27, with higher scores indicating severe depression).[41] The Columbia-Suicide Severity Rating Scale (severity of ideation subscale score range: 0-5, with higher scores indicating presence of ideation with at least some intent to die)[42,43] was completed at every visit to assess for potentially worsening suicidal ideation throughout the trial. Anxiety symptoms were measured using the clinician-administered Hamilton Anxiety Rating Scale (score range: 0-56, with higher scores indicating severe anxiety)[44] and the State-Trait Anxiety Index (score range: 0-80, with higher scores indicating greater anxiety).[45] Blood pressure and heart rate were examined before and during the psilocybin sessions.

Statistical Analysis

Data analysis was conducted on participants who completed the intervention (evaluable population). A previous study of psilocybin[16] found a large effect of a high psilocybin dose (com-

Table. Characteristics of the Overall Sample and Comparison of Baseline Demographic and Background Characteristics Between Participants in the Immediate and Delayed Treatment Condition Groups

Characteristic	No. (%)			χ^2 or *t* Value[a]	*P* value[a]
	Overall sample (N = 24)	Immediate treatment (n = 13)	Delayed treatment (n = 11)		
Age, mean (SD), y	39.8 (12.2)	43.6 (13.0)	35.2 (9.9)	−1.8	.08
Time with depression, mean (SD), y	21.5 (12.2)	23.5 (12.7)	19.2 (11.8)	−0.86	.40
Time in current major depressive episode, mean (SD), mo[b]	24.4 (22.0)	25.9 (22.4)	22.6 (22.5)	−0.36	.39
Lifetime psychedelic use	0.8 (1.9)	0.5 (1.7)	1.3 (2.2)	1.02	.32
Female sex	16 (67)	9 (69)	7 (64)	1.34	.39
Heterosexual orientation	21 (96)	13 (100)	8 (89)	1.51	.41
White race/ethnicity	22 (92)	13 (100)	9 (82)	2.58	.20
Educational level					
<College	2 (8)	0 (0)	2 (18)		
Associate's degree	2 (8)	1 (8)	1 (9)		
Bachelor's degree	14 (58)	7 (54)	7 (64)	4.32	.41
Master's degree	4 (17)	3 (23)	1 (9)		
Advanced degree	2 (8)	2 (15)	0 (0)		
Marital status					
Married/living with partner	11 (46)	6 (46)	5 (46)		
Divorced/separated	1 (4)	1 (8)	0 (0)	0.94	>.99
Never married	12 (50)	6 (46)	6 (55)		
Employment status					
Full-time	15 (63)	8 (62)	7 (64)		
Part-time	4 (17)	3 (23)	1 (9)	1.13	.73
Unemployed	5 (21)	2 (15)	3 (27)		

[a] χ^2, *t*, and *P* values refer to tests for differences between the immediate treatment and delayed treatment conditions.

[b] Major depressive episode was defined by the *DSM-5*.

pared with a low dose) on reducing GRID-HAMD scores (Cohen *d* = 1.30). Assuming a similar large effect size with 24 participants, nearly 100% power was calculated to detect a statistically significant effect of psilocybin on change in depressive symptoms.

No primary outcome data were missing. Descriptive statistics for demographic and background characteristics for all study variables were calculated and compared between study conditions using a 2-sample *t* test for continuous variables and a χ^2 test for all remaining variables. A repeated-measures analysis of variance with time (baseline, week 5, and week 8) and condition (immediate treatment and delayed treatment) as factors was used to examine changes in the primary depression outcome (GRID-HAMD score).

Follow-up planned comparisons included independent samples *t* tests to compare week 1 with week 4 GRID-HAMD scores in the immediate treatment condition group (corresponding to the week 5 and week 8 time points in the delayed treatment condition group). Within-participant (n = 24) treatment effect was examined using *t* tests comparing GRID-HAMD scores at baseline with scores at week 1 and week 4 postsession-2 follow-up. Rapid and sustained antidepressant effects were examined using *t* tests comparing QIDS-SR scores between baseline and day 1 postsession-1 and between baseline and week 4 postsession-2 follow-up. Effect sizes for the independent samples *t* tests were calculated using the Cohen *d* statistic, and effect sizes for the repeated-measures analysis of variance were calculated using the partial eta squared (η_p^2) statistic. Further primary outcomes included a descriptive analysis of the percentage of participants who met the criterion for clinically significant response and remission in the sample.

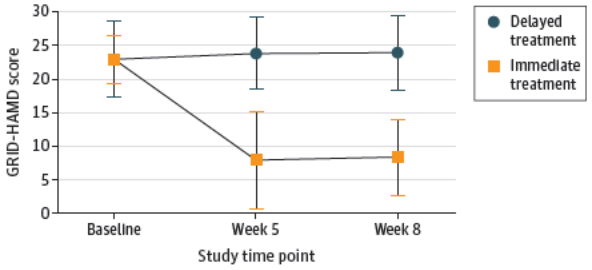
All statistical tests used a $P < .05$ to determine statistical significance. Data analysis was conducted from July 1, 2019, to July 31, 2020, using SPSS, version 25 (IBM).[46] Data analysis plans for secondary outcomes are reported in the eMethods in Supplement 2.

Results

A total of 27 participants were randomized, of whom 24 (89%) completed the intervention as well as the postsession assessments at weeks 1 and 4; specifically, 13 were randomized to the immediate treatment group and 11 to the delayed treatment group (Figure 1). The **Table** shows the demographic characteristics for the 24 participants, among whom were 16 women (67%) and 8 men (33%), with a mean (SD) age of 39.8 (12.2) years and a mean (SD) baseline GRID-HAMD score of 22.8 (3.9). An examination of the differences in stratification variables as a function of the treatment condition indicated no statistically significant differences between conditions (mean [SD] months in current major depressive episode: immediate treatment, 25.9 [22.4]; delayed treatment, 22.6 [22.5]; $P = .39$) (Table).

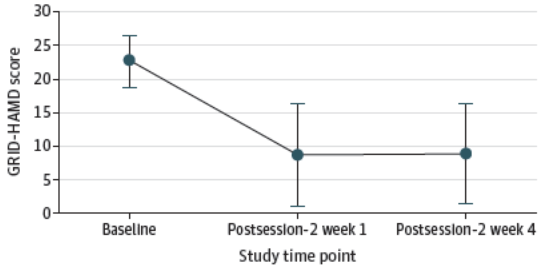
A statistically significant time by condition interaction effect on GRID-HAMD was found ($\eta_p^2 = 0.57$; 90% CI, 0.38-0.66; $P < .001$) (**Figure 3**).

Figure 3. Comparison of GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores Between the Delayed Treatment and Immediate Treatment Groups



Data points are presented as mean (SD). In the immediate treatment group (n = 13), weeks 5 and 8 correspond to weeks 1 and 4 after the psilocybin session 2. In the delayed treatment group (n = 11), weeks 5 and 8 are prepsilocybin assessments obtained during the delay period. Effect sizes (Cohen *d* with 95% CI) and *P* values reflect the results of a 2-sample *t* test between the 2 groups at week 5 (Cohen *d* = 2.5; 95% CI, 1.4-3.5; *P* < .001) and week 8 (Cohen *d* = 2.6; 95% CI, 1.5-3.7; *P* < .001).

Figure 4. Decrease in the GRID Hamilton Depression Rating Scale (GRID-HAMD) Scores at Week 1 and Week 4 Postsession-2 Follow-up in the Overall Treatment Sample



The mean (SD) GRID-HAMD score was 22.8 (3.9) at baseline, 8.7 (7.6) at week 1, and 8.9 (7.4) at week 4. Effect sizes (Cohen *d* with 95% CI) and *P* values reflect the results of a paired sample *t* test that compared scores between baseline and week 1 (Cohen *d* = 2.3; 95% CI, 1.5-3.1; *P* < .001) and week 4 postsession-2 follow-up (Cohen *d* = 2.3; 95% CI, 1.5-3.1; *P* < .001).

Follow-up independent samples *t* tests revealed significantly lower depression scores in the immediate treatment condition at weeks 1 and 4 postsession-2 follow-up compared with the corresponding time points (weeks 5 and 8) in the delayed treatment condition before psilocybin treatment. In the immediate treatment group, the mean (SD) GRID-HAMD scores were 22.9 (3.6) at baseline, 8.0 (7.1) at week 5, and 8.5 (5.7) at week 8. In the delayed treatment group, the mean (SD) GRID-HAMD scores were 22.5 (4.4) at baseline, 23.8 (5.4) at week 5, and 23.5 (6.0) at week 8. The effect sizes were large at week 5 (Cohen *d* = 2.5; 95% CI, 1.4-3.5; *P* < .001) and at week 8 (Cohen *d* = 2.6; 95% CI, 1.5-3.7; *P* < .001) (eTables 1-3 and eResults in Supplement 2).

After the psilocybin session, 17 participants (71%) at week 1 and 17 participants (71%) at week 4 had a clinically significant response to the intervention (≥50% reduction in GRID-HAMD score), and 14 participants (58%) at week 1 and 13 participants (54%) at week 4 met the criteria for remission of depression (≤7 GRID-HAMD score). Within-participant *t* tests showed statistically significant decreases in GRID-HAMD scores among participants from baseline to week 1 (Cohen *d* = 2.3; 95% CI, 1.5-3.1; *P* < .001) and week 4 (Cohen *d* = 2.3; 95% CI, 1.5-3.1; *P* < .001) (**Figure 4**). The QIDS-SR measure of depression, which was assessed more frequently, showed a rapid, large decrease in mean (SD) depression score among participants from baseline to day 1 after psilocybin session 1 (16.7 [3.5] vs 6.3 [4.4]; Cohen *d* = 2.6; 95% CI, 1.8-3.5; *P* < .001). This substantial decrease remained through week 4 after session 2 (6.0 [5.7]; Cohen *d* = 2.3; 95% CI, 1.5-3.0; *P* < .001) (eFigure 1 in Supplement 2).

All secondary depression and anxiety outcomes showed a similar pattern of results as the primary depression outcomes, with statistically significant differences between conditions and across both conditions after entry into the active intervention period (eTables 1 to 3 and eFigures 1 to 8 in Supplement 2). For example, statistically significant treatment condition effects were found on self-reported depression (Beck Depression Inventory II and Patient Health Questionnaire-9) and clinician-administered anxiety (Hamilton Anxiety Rating Scale) measures. Overall, suicidal ideation was low and trended lower after enrollment in both groups (eFigure 9 in Supplement 2).

Participant and facilitator rated intensity of acute psilocybin effects are provided in eTables 4-6 in Supplement 2. There were no serious adverse events in this trial. A transient increase in blood pressure that exceeded the protocol criteria for more frequent assessment (ie, diastolic blood pressure >100 mm Hg) occurred during 1 session, but no medical intervention was needed, and the blood pressure level remained within predetermined safety parameters and resolved spontaneously during the session (eTable 7 in Supplement 2). Other nonserious adverse effects, which occurred during the psilocybin administration, that were reported by participants after completing at least one-half of the psilocybin sessions included challenging emotional (eg, fear and sadness) and physical (eg, feeling body shake or tremble) experiences (eTable 8 in Supplement 2). Mild to moderate transient headache was reported during 16 of 48 sessions (33%) and after the subjective psilocybin effects had subsided after 14 of 48 sessions (29%). Other adverse events are reported in eTables 8 and 9 in Supplement 2, and initiation of antidepressants or psychotherapy is reported in eTable 10 in Supplement 2.

Discussion

This randomized clinical trial documented the substantial rapid and enduring antidepressant effects of psilocybin-assisted therapy among patients with MDD. Although the rapid antidepressant effects of psilocybin are similar to those reported with ketamine,[10,11] the therapeutic effects are different: ketamine effects typically last for a few days to 2 weeks, whereas the current study showed that clinically significant antidepressant response to psilocybin therapy persisted for at least 4 weeks, with 71% of the participants continuing to show a clinically significant response (≥50% reduction in GRID-HAMD score) at week 4 of follow-up. Furthermore, psilocybin was

found to have low potential for addiction[22] and a minimal adverse event profile,[22,23] suggesting therapeutic advantages with less risk for associated problems than ketamine.[12] The present findings in patients with MDD are consistent with results of studies that reported on the effectiveness of psilocybin-assisted therapy in producing antidepressant effects among patients with cancer who had psychological distress[16,17,47] and a small open-label study of patients with treatment-resistant depression.[18]

The mounting evidence of the use of psilocybin as an adjunct to treatment of a variety of psychiatric conditions (eg, depression,[16-18] tobacco use disorder,[48] and alcohol use disorder[49]) suggests a transdiagnostic mechanism of action. In several studies in patients[16-18,49-51] and in healthy volunteers,[32,52] the intensity of mystical-type experiences reported after psilocybin sessions was associated with favorable outcomes. Furthermore, cross-sectional studies have suggested that mystical-type and psychologically insightful experiences during a psychedelic session predict positive therapeutic effects.[53-55] Consistent with these previous studies, the current trial showed that psilocybin-occasioned mystical-type, personally meaningful, and insightful experiences were associated with decreases in depression at 4 weeks (eResults in Supplement 2). Furthermore, a recent report suggested that psilocybin may decrease negative affect and the neural correlates of negative affect,[56] which may be a mechanism underlying transdiagnostic efficacy. Taken together, these findings suggest that further studies into psychological and neural mechanisms across different psychiatric conditions are warranted.

The present trial showed that psilocybin administered in the context of supportive psychotherapy (approximately 11 hours) produced large, rapid, and sustained antidepressant effects. The effect sizes reported in this study were approximately 2.5 times greater than the effect sizes found in psychotherapy[57] and more than 4 times greater than the effect sizes found in psychopharmacological depression treatment studies.[58] These findings are consistent with literature that showed that combined pharmacotherapy and psychotherapy were more efficacious in the treatment of MDD than either intervention alone.[59-61] Furthermore, given that psilocybin was associated with nonserious adverse effects that were frequently reported as mild-to-moderate headache and challenging emotions that were limited to the time of sessions (eTables 8 and 9 in Supplement 2), this intervention may be more acceptable to patients than widely prescribed antidepressant medications that confer substantially more problematic effects (eg, suicidal ideation, decrease in sexual drive, and weight gain). The effectiveness of psilocybin therapy after a single or only a few administrations represents another substantial advantage over commonly used antidepressants that require daily administration.

Strengths and Limitations

This study has some strengths. It had a randomized design and used GRID-HAMD as the primary outcome measure that was assessed by blinded clinician raters. The delayed treatment condition controlled for the possible effects of having been accepted into the trial and for the passage of time between screening and initial follow-up assessments. However, the delayed treatment condition did not control for other aspects of psilocybin administration, such as preparation and rapport building, postsession integration meetings, or expectancy effects. Although placebo and active treatment controlled designs are widely used in therapeutic trials,[62] they too have limitations owing to the highly discriminable effects of psilocybin.

This study has some other limitations. It had a short-term follow-up, a small sample that was predominantly composed of White non-Hispanic participants, and included participants with low risk of suicide and moderately severe depression. Further research with larger and more diverse samples, longer-term follow-up, and a placebo control is needed to better ascertain the safety (eg, abuse potential of psilocybin, suicide risk, and emergence of psychosis) and efficacy of this intervention among patients with MDD. Another limitation is the psychotherapy approach[31] that involved session facilitators from a variety of professional disciplines (eg, social work, psychology, psychiatry) and session facilitators without formal clinical training (eg, research assistants and clinical trainees). The type of psychotherapy offered and the characteristics of therapists should be explored in future studies.

Conclusions

Results of this randomized clinical trial demonstrated the efficacy of psilocybin-assisted therapy in producing large, rapid, and sustained antidepressant effects among patients with MDD. These data expand the findings of previous studies involving patients with cancer and depression as well as patients with treatment-resistant depression by suggesting that psilocybin may be effective in the much larger population of MDD. Further studies are needed with active treatment or placebo controls and in larger and more diverse populations.

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Individual Experiences in Four Cancer Patients Following Psilocybin-Assisted Psychotherapy

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A growing body of evidence shows that existential and spiritual well-being in cancer patients is associated with better medical outcomes, improved quality of life, and serves as a buffer against depression, hopelessness, and desire for hastened death. Historical and recent research suggests a role for psilocybin-assisted psychotherapy in treating cancer-related anxiety and depression. A double-blind controlled trial was performed, where 29 patients with cancer-related anxiety and depression were randomly assigned to treatment with single-dose psilocybin (0.3 mg/kg) or niacin in conjunction with psychotherapy. Previously published results of this trial demonstrated that, in conjunction with psychotherapy, moderate-dose psilocybin produced rapid, robust, and enduring anxiolytic, and anti-depressant effects. Here, we illustrate unique clinical courses described by four participants using quantitative measures of acute and persisting effects of psilocybin, anxiety, depression, quality of life, and spiritual well-being, as well as qualitative interviews, written narratives, and clinician notes. Although the content of each psilocybin-assisted experience was unique to each participant, several thematic similarities and differences across the various sessions stood out. These four participants' personal narratives extended beyond the cancer diagnosis itself, frequently revolving around themes of self-compassion and love, acceptance of death, and memories of past trauma, though the specific details or narrative content differ substantially. The results presented here demonstrate the personalized nature of the subjective experiences elicited through treatment with psilocybin, particularly with respect to the spiritual and/or psychological needs of each patient.

Keywords: end-of-life, anxiety, depression, psilocybin, psychedelics, hallucinogen

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INTRODUCTION

From the early 1960s–1970s, psychedelic drug-assisted psychotherapy was researched in the United States as a treatment for cancer-related psychological and existential distress. These trials included several hundred participants and showed improvements in depression, anxiety, fear of dying, quality of life, and pain (Kast and Collins, 1964; Kast, 1966; Pahnke, 1969; Grof et al., 1973b). Building upon this research, several recently published trials examining psilocybin to treat cancer-related psychological and existential distress demonstrated rapid, substantial, and sustained improvements in cancer-related anxiety and depression, existential

distress, quality of life, and orientation toward death (Grob et al., 2011; Griffiths et al., 2016; Ross et al., 2016).

To better understand participant experiences, in-depth interviews were conducted with 13 participants treated in the Ross et al. (2016) trial, revealing several common themes related to the psilocybin experience (Belser et al., 2017; Swift et al., 2017). Here, we have selected four participants from this trial (Ross et al., 2016) whose psilocybin session included several of the themes reported in the published qualitative studies of patient experiences. We demonstrate how variable and personalized participants' psilocybin experiences were, while still representing a relatively small number of overarching themes. The case report method is unique in that it facilitates the exploration of idiographic phenomena pertaining to the explication of individual cases. It lies between the methodologies of controlled clinical trials and qualitative methods, and complements both by incorporating quantitative and qualitative information. The psychological processes described will inform the design, measures, and hypotheses of future trials. The authors sought to illustrate some of the individualized symptoms, experiences, and clinical courses that are difficult to present using traditional reporting methods. While previously published summary data from this trial demonstrate reductions in anxiety, depression, and psychosocial distress associated with death and dying, as well as common qualitative experiential themes, the current report aims to elucidate the rich complexity and personalized nature of patient responses to psilocybin-assisted psychotherapy.

METHODS

Data from this report were collected in a completed double-blind randomized controlled trial of psilocybin-assisted psychotherapy of anxiety and depression in cancer patients (see Ross et al., 2016; Supplementary Methods and **Supplementary Figure S1** for an overview of study design) and two studies utilizing qualitative analysis of interviews from a subset of participants in the main trial (see Belser et al., 2017; Swift et al., 2017 for description of emergent themes). We present quantitative as well as qualitative data collected through participant interviews, participant-completed surveys, and notes from study therapists. See Supplementary Materials for description of the quantitative measures presented.

Various demographic data, including but not limited to names, age, and type of cancer, have been obscured to preserve anonymity. The participants presented provided written informed consent for publication of these de-identified reports and were selected to demonstrate their unique experiences and because they each benefited from the treatment in different ways.

RESULTS

Quantitative clinical anxiety and depression results for these participants are presented in **Figure 1**, demographic information for each participant are presented in **Table 1**, and cancer-related measures of demoralization, hopelessness, and attitudes toward death are shown in **Supplementary Figure S2**. Each participant described here demonstrated improvement on multiple measures, regardless of the content of their experience.

Victor

Victor was a male in his 20s employed as a full-time graduate student at enrollment. He was raised Jewish, but renounced his faith when he was diagnosed with non-Hodgkin's lymphoma during his sophomore year of high school. At the time of his diagnosis, Victor felt that "God had failed him," and that his "sense of bodily invulnerability had been shattered." When he enrolled in the trial, he was a self-described atheist and had used LSD previously. Victor was in remission at the time of enrollment but was afflicted by anxiety and fear of possible recurrence. His study therapists noted that Victor described severe anxiety, including intermittent panic attacks and constant worry about his survival. At screening, he was diagnosed with Adjustment Disorder with Anxiety, Chronic.

At the start of his psilocybin session, Victor reported seeing "geometric patterns," with his eyes closed. He was then led on a journey by a felt presence, what he described as a "spirit guide." "I would experience a different emotion in each part of the experience, and when that emotion became overwhelming... This spiritual guide came in through the music." He witnessed his own conception, birth, and death, and described a vision in which he watched his family at his own funeral while feeling a "tremendously painful" helplessness. Victor noted that his session was dominated by emotional experiences and that, "whenever the affect would become overwhelming. . . the spirit guide would blast me out of that experience into a new setting." Victor then said, "I didn't have a body. . . I was just like this soul, this entity," and spoke of himself shopping for a new body. The only body he could pick was his own, what he later described as a representation of the resolution of his issues with his body and illness.

> I saw everything that has happened to my body, all the food I have eaten, the drugs I have taken, the alcohol [I have drunk], the people I have had sex with, the chemo, the exercise, everything that has ever happened to my body. I took it in at once, then I made this decision. Like okay, I need a body to go on, so I will choose this body. So I kind of accepted this body, and at this point I was no longer this soul spirit entity. It became me, integrated my mind into my body.

After Victor chose his body, he recalled, "there was something on top of the mountain, call it God, call it some divine entity calling me to come up this mountain. . . it was like a spiritual calling." Victor asked his "spirit guide" if he could meet him. Ultimately, the "spirit guide" returned and said that God wouldn't meet with him yet, but delivered a message that if Victor is loving and kind to other people, he might be able to meet God one day. Toward the end of the session, the "spirit guide" transformed into Victor's father, who reassured him that everything was going to be okay. Before the end of his session, he encountered several people who he loved that had passed away, and they all shared their love for him.

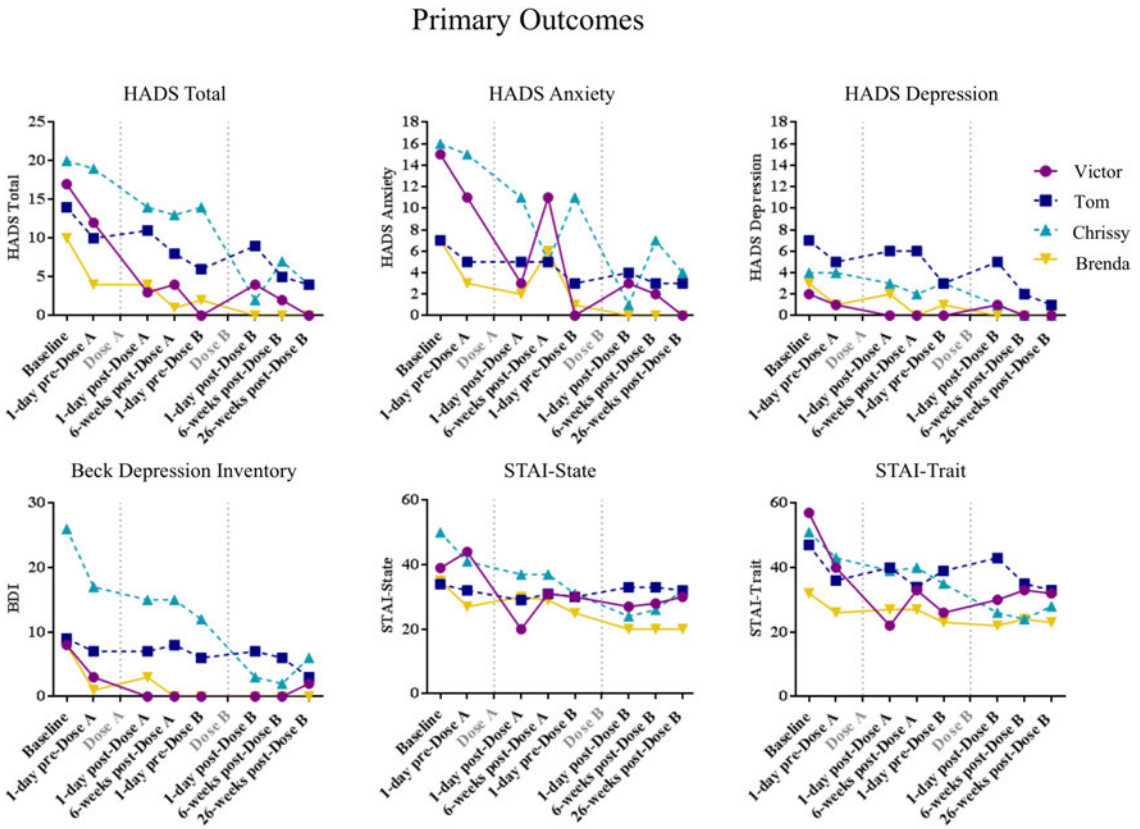

FIGURE 1 | Quantitative data from the four cases presented. Scores on the Hospitalized Anxiety and Depression Scale (HADS), the Beck Depression Inventory (BDI) and the Spielberger State-Trait Anxiety Inventory (STAI) are shown here for each participant over time.

TABLE 1 | Patient demographics and pre-treatment history.

Participant	Victor	Tom	Chrissy	Brenda
Age	20s	50s	50s	60s
Gender	Male	Male	Female	Female
Race	White or Caucasian	White or Caucasian	White or Caucasian	White or Caucasian
Disease Site	Lymphoma (non-Hodgkins)	Chronic Myeloid Leukemia	Breast	Colon
Stage	IIIa	Other	IV	I
Prior Hallucinogen Use	Yes	No	Yes	No
Marital Status	Never Married	Married	Never Married	Cohabitation
Education	Completed 4-year College	Completed Grad/Professional School	Part College	Completed Grad/Professional School
Employment	Full-Time Student	Full-Time Employed	Full-Time Employed	Full-Time Employed
Religious/Spiritual Beliefs	Atheist/Agnostic	Christian	Atheist/Agnostic	Atheist/Agnostic
SCID Diagnosis	Adjustment Disorder with anxiety, chronic	Adjustment Disorder with anxiety, chronic	Generalized Anxiety Disorder	Adjustment Disorder with anxiety, chronic
Psilocybin Treatment Randomization	First Session	Second Session	Second Session	First Session

His data showed decreased anxiety, and increased purpose in life, spirituality and death transcendence. In a follow-up interview, Victor stated "I would say [I have] less anxiety about my body and my sickness coming back, my cancer coming back. . .I saw this body for what it's worth, I picked it, it's mine. . . I think that acceptance has been liberating." With regards to his increased spirituality, Victor stated, "I am convinced beyond any doubt that there is a spiritual realm. . .The spirit guide showed me a world that I believe to be very, very real." When asked how the experience changed his attitude toward his cancer, he responded, "It is what it is. . .it's not worth worrying about things you can't change."

Tom

Tom was a Christian male in his 50s employed full-time in human resources upon screening. Shortly before enrolling in our trial, Tom was diagnosed with Chronic Myeloid Leukemia. At screening, he met diagnostic criteria for Adjustment Disorder with Anxiety, Chronic. Tom had never used hallucinogens at the time of enrollment.

During his psilocybin session, Tom reported seeing an inhuman, aggressive female face that he felt would bite him, given the chance. The female face transformed into a less-threatening male figure that invited him to "start" his psychedelic experience. Following this, Tom explained how the music from the study's preselected playlist influenced his experience. "I started not just hearing, but playing the music. My entire body was the musical instrument for every sound which was coming through my head." At one point, he removed his eye-shades to go to the bathroom and described seeing strobe-like flashing colors. He experienced visual-auditory synesthesia; he described "seeing" the music as red, blue, and green three-dimensional abstract shapes. For the next part of his experience, Tom described a sense of all-knowingness, "There is nothing to fear after you stop being in your body . . .it's absolutely no hell or heaven, it's just nothing to be afraid of." He also detailed being surrounded by an "overwhelming feeling of love... I felt the urge to let people know to stop silly things and that nothing matters but love." Tom described his experience as exhausting, but felt that he gained a greater appreciation for life and simultaneously lost his fear of death.

Tom showed moderately decreased anxiety and depression, hopelessness, demoralization, and death anxiety. "I don't have a fear of death – I mean, I don't have any desire to die. . .I am more interested in life now more than ever before. . .death in itself does not scare me," he stated. His religiousness and spirituality data showed insignificant changes, which is illustrated qualitatively in his follow-up interview: "It was not religious in a traditional sense at all, I mean there was no religious figures." Though Tom experienced moderate benefits in anxiety, depression, demoralization, and death anxiety, he was underwhelmed and disappointed with the psilocybin experience, its short-term effects, and its impact on his life. When asked about how his experience has affected his life, he replied, "to be honest with you, not much. . .I mean, it was intense, it just. . .was not life-changing, and I heard, for some other people, that it was." However, despite his lackluster claim, he admitted that he discovered, "there's nothing but love. Like the Beatles did sing, 'All you need is love,' that's very true."

Chrissy

Chrissy was a female in her 50s, diagnosed with stage 4 breast cancer with metastases in her lungs. She was a self-described atheist and employed full-time as an administrative supervisor in the healthcare industry at baseline. She had never been married nor had children, and she lived alone. She had used both psilocybin and LSD in her past, and received a diagnosis of Generalized Anxiety Disorder upon screening.

During her qualitative interview, Chrissy said that she knew she was beginning to experience the psilocybin effects when she could "see music," something she described as beautiful, comforting and amazing. She remembers being surrounded by the cosmos, spirits and light, and hearing words inside her head, in a voice different from her own, saying, "we are here all together," a phrase she interpreted as welcoming her into this psilocybin-induced state. She describes a part of her experience:

> I was seeing these kind of stone faces, and they were beautiful, and they would kind of come to dust, and then they would come back up, and then they would come back to dust, so I kind of think of that as like, that's the nature of life. . . it rises and falls; that's the normal way it is.

Chrissy experienced strong themes of unity and connection during this session as demonstrated by the following quote: "I felt like I could reach out to anybody and connect with them." At one point, Chrissy saw a Ferris wheel, which she interpreted as a circle in which "life comes from death and death comes from life." Chrissy experienced her own birth and explained, "I remember breathing, feeling my breathing, and then kind of feeling that I was coming up against a membrane of some sort. Then at some point, I came through to it, and that was just amazing." She spoke about feeling pain in her abdomen, where her cancer was, and experienced this as her "umbilical cord to the universe." She expressed, "this was where my life would be drained from me some day and I would surrender willingly when my time came." Though Chrissy experienced a sense of being at peace with death, she went on to explain that she "chose to live," and that the experience helped her reach this decision.

Chrissy experienced significantly decreased anxiety, depression, death anxiety, hopelessness, demoralization, and increased purpose in life, spirituality, and death transcendence. Chrissy said, "At one point I asked, 'Is there going to be a cure for cancer?' [It] doesn't matter. We're all going to die – doesn't change it. That was my answer." When prompted on a follow-up questionnaire whether her religious or spiritual beliefs had changed since her psilocybin session, she replied, "[The psilocybin experience] brought my beliefs to life, made them real, something tangible and true – it made my beliefs more than something to think about, really something to lean on and look forward to."

Brenda

Brenda was a female in her 60s who had stage I colon cancer, her second lifetime cancer diagnosis (she was in remission from uterine cancer) at enrollment. She was a full-time working professional and identified as an atheist at the time of her enrollment. Brenda was divorced and had two adult children. Upon screening, she identified as hallucinogen-naïve and met criteria for Adjustment Disorder with Anxiety, Chronic.

Brenda's psilocybin experience was a "roller-coaster kind" of train ride. She described the music as being an important catalyst throughout her journey. She discussed a comforting "whirring" sound throughout the beginning of her experience that she felt was "taking her in." At one point, Brenda felt she was contently lying on a damp cloud and thought to herself, "If this is the way

it's going to be, it's going to be really interesting. This is going to be really amazing. And I'm ready to go." From there, she described feeling outside of time and space, "I felt out of space and time in a way that was really, really, really comforting and beautiful." Brenda described an experience of interconnectedness and unity, "I was the cloud, I was everything, and that was the theme throughout the whole [experience], that I was all this –this was me. And it was so wonderful. . . to believe that. And I still do- that is me."

Brenda also felt as if she experienced her own death on two separate occasions during the experience and emerged both unafraid of death and viewing it as a beautiful component of existence. On the first occasion, she said, "I went into this black area and it was just wonderful... I just thought to myself... I think this might be what people experience when they die." Her second encounter with death included seeing, "This brick thing that was a lot of bricks, and I realized this was a kind of crematorium... I was just part of this big beautiful world... and that's what's going to happen when I die... maybe death is a beautiful thing."

Her experience also unearthed childhood memories of sexual assault that she realized remained unhealed. Brenda acknowledged the study as a catalyst to begin healing from this trauma. Her data depicted decreased anxiety and death anxiety. When questioned on how the session altered her life, she responded, "What's so funny is that nobody can really see it, but yet, for me, everything has changed. . .I feel more contented and happy about my place in the world in all the things I'm doing." Her data also showed an increase in spirituality, as illustrated in her follow-up interview; "So I think that's also opened up to me tremendously – a spiritual piece. And I've never been religious; I'm not religious particularly at all. And I feel like I've really connected with a spiritual side in myself as well." After the trial, Brenda became interested in pursuing her relationship with this new aspect of herself, and began seeking out opportunities to recollect and re-experience elements of the experience through meditation. She said:

> I've been exploring whether I can bring back other sensations from it. . .I have been able to, and I've been doing a lot of meditating. I got into meditating afterward because it was like, 'I just don't want to lose this,'. . .I have a house up by a mountain monastery and I went up there, and that was very comforting to connect that way. . . I really felt like there was a real connection with Buddhism and meditation and the psilocybin experience for me. And I've been doing that everyday.

CONCLUSION

The cases presented here were selected because their experiences were unique, but also represented several themes identified in published qualitative studies from this trial. These descriptions are not meant to be generalized. However, several broad conclusions can be drawn from these cases. Primarily, none of these participants had an experience dominated by any single theme. Rather, their experiences were rich in multiple thematic areas, while still retaining personal, meaningful, and tangible content. These four participants presented with varied psychological needs at enrollment, including symptoms of anxiety, depression, and other measures of existential distress. These distinct needs were met post-psilocybin treatment, and benefits were sustained throughout follow-up, regardless of the thematic content of their experience (**Figure 1** and **Supplementary Figure S2**).

Participants often had difficulty describing the episodic content of their medication sessions, and the emotional and cognitive impact of the experience was often easier to describe than specific content. This could be due to an inherent ineffability of the experience, or to participants' lack of articulateness and/or vocabulary. Regardless, whether or not a psychedelic experience can be verbally described does not seem to predict its meaningfulness or clinical impact. In fact, descriptions of the psychedelic experience were frequently given in terms of how it made participants feel and how it restructured their thinking and emotional responses in everyday life, which may be more important for persisting benefit than any specific content. While visual/auditory alterations have not been demonstrated to predict clinical change, these perceptual effects do not seem to negate the benefit of other content. Although mystical experience was found to mediate the clinical benefit reported by participants in this trial (see Supplementary Materials; Ross et al., 2016 for discussion), this does not preclude the existence of other additional mediators. The experiences described herein suggest that there may be other mediators of the therapeutic potential of psilocybin-assisted psychotherapy.

Several other questions remain unanswered and should be the focus of future trials. Participant experiences did not necessarily focus on cancer, and included salient feelings of self-compassion and love, acceptance of death, new appreciation for life, and memories of past trauma. This raises the question of whether one has to be imminently facing death to gain benefit from such treatment. Lasting behavioral changes, including eating healthier, increased exercise, and non-drug spiritual and/or meditative practices were reported by all four of the participants presented here. Whether non-drug methods of altering consciousness following psychedelic-assisted psychotherapy are helpful as an adjunct to psilocybin-induced altered states of consciousness is an important question for future studies to explore.

Not only did these experiences meet each person's psychological needs, they also helped them understand what their needs were. Thus, one therapeutic function of psilocybin may be to assist participants in achieving insight into the cause of their distress, which is supplemented by our supportive and integrative psychotherapy treatment model. The predominant view within psychedelic research is that both psychedelic medication and psychotherapy are necessary for benefits to be reported by study participants. It is likely that the clinical benefit following treatment with psilocybin versus niacin in the current trial was a result of this drug-therapy interaction. The model employed in the current trial was most similar to "psychedelic-peak therapy" from the 1950s through 1970s (Sherwood et al., 1962; Hoffer, 1967; Pahnke et al., 1970; Grof et al., 1973a). Other models utilized in psychedelic research include the psychedelic-chemotherapy model, which used a

single high-dose session of psychedelic treatment with minimal psychotherapy (e.g., Hollister et al., 1969), and the psycholytic model, which used repeated lower doses of psychedelics along with psychodynamic psychotherapy (Pahnke et al., 1970). While we have demonstrated the therapeutic value of our treatment model, future trials will be needed to evaluate comparative efficacy of the various psychotherapeutic models that have been historically used, and to answer the many remaining questions regarding optimization of psychedelic-assisted psychotherapy.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the institutional review board of the New York University School of Medicine (NYUSoM), with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the institutional review board of the NYUSoM.

AUTHOR CONTRIBUTIONS

SR was the principal investigator of the parent trial that served as the platform for the data collection presented in this manuscript. JG, APB, and SR acted as study therapists for the parent trial that served as the platform for the data collection presented in this manuscript. TM, AB, and GA-L acted as study coordinators and/or performed data collection for the parent trial that served as the platform for the data collection presented in this manuscript. SM, TM, SP, and LO contributed to the drafting of this manuscript. All authors contributed to the conceptualization and writing and approved the final version of this manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2018.00256/full#supplementary-material

FIGURE S1 | Overview of study design. Treatment components by week are depicted.

FIGURE S2 | Quantitative data from the four cases presented. Scores on the Death Anxiety Scale (DAS), the Hopelessness and Anxiety Inventory (HAI), the Purpose in Life (PIL) questionnaire, the Death Transcendence Scale (DTS), the Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-SWB) and the Spiritual Transcendence Scale (STS) are shown here for each participant over time.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Palliative Care Division

UR MEDICINE

February 20, 2020

Re: STATEMENT SUPPORTING OREGON'S MEASURE 34, THE PSILOCYBIN SERVICE INITIATIVE, ENABLING ACCESS FOR PALLIATIVE CARE IN TERMINALLY ILL PATIENTS

To Whom It May Concern:

I am a medical doctor specializing in the palliative care of seriously ill patients many of whom are dying of terminal illnesses. I hold the position of Distinguished Professor of Palliative Care, and Professor of Medicine, Psychiatry, Medical Humanities and Nursing at the University of Rochester School of Medicine (URMC). I am the Founding Director of the URMC Palliative Care Program and Acting Director of the URMC Center for Bioethics. I am a board certified palliative care consultant.

I have published and lectured widely about end-of-life care and exploring last-resort options. I am the author of several books on end-of life including Caring for Patients at the End of Life: Facing an Uncertain Future Together (Oxford University Press, 2001), and A Midwife Through the Dying Process: Stories of Healing and Hard Choices at the End of Life (Johns Hopkins University Press, 1996), as well as numerous articles published in major medical journals. I am a Fellow in the American College of Physicians and in the American Academy of Hospice and Palliative Medicine, an ABMS certified Palliative Care consultant, and past President of the American Academy of Hospice and Palliative Medicine.

Those of us providing palliative and end of life care have been pleased to see important advancements in the care of the dying over the past 30 years. Terminally ill patients are more likely to get aggressive pain and symptom management, hospice is much more widely available, and patients have more choices about treatment at the end of life. Yet, most of this progress has been made in addressing

physical suffering, and much less has emerged to address nonphysical suffering. This is why it is so important to support making psychotherapy facilitated with psilocybin available.

Recent clinical trials demonstrate the powerful therapeutic use of psilocybin in relieving refractory anxiety and depression in terminally ill patients. Many patients with advanced-stage cancer suffering from treatment resistant anxiety and/or depression experienced significant reductions in both anxiety and depression with improvements of mood following a single guided psilocybin treatment, with relatively minimal adverse events. Other studies demonstrate efficacy of other similar agents to relieve anxiety and stress disorders related to end of life. Therapy with psilocybin is generally well tolerated by seriously ill patients who have chosen to try it, and remarkably effective in alleviating non-physical distress. Therapeutic benefits often persist long after any pharmacologic effect of the drug. It is time to allow the legitimate therapeutic use of psychedelic medicine.

These findings are especially exciting in light of the fact that efforts of the past quarter century to enhance palliative care for the terminally ill have yielded significant progress in reducing physical pain and discomfort, relatively little progress has been made in helping patients reduce anxiety or depression about, or come to terms with, the psychological and existential issues raised by impending death. Psychotherapy facilitated with psilocybin offers an additional palliative care tool to improve the wellbeing of terminally ill patients by mitigating psychological distress.

As you may know, I have been a long term advocate for more and better palliative care for all seriously ill patients, and for open access to a physician assisted death for those terminally ill patients who competently request it because of suffering that has become unacceptable to them despite unrestrained efforts to palliate. In the debates about whether or not to enact a law permitting this practice, known as "medical aid in dying", virtually everyone agreed that eligible patients be provided with excellent palliative care using all potentially effective measures to ensure that no patient was motivated to choose to precipitate death due to inadequate pain and symptom management. Even Dr. Ira Byock, a staunch opponent of allowing access to physician assisted death, supports giving dying patients access to these promising treatments (Byock I. Taking Psychedelics Seriously. J Palliative Med. 2018;21:4. 417-21).

Adding another intervention to the 'tool box' of potentially effective palliative measures available to terminally ill patients is critically important in this process of ensuring dying patients have access to the full range of potentially effective palliative treatments to address uncomfortable symptoms.

For all these reasons, I support making psychotherapy facilitated with psilocybin available to terminally ill patients suffering anxiety and depression.

Respectfully,

Timothy E. Quill MD, MACP, FAAHPM

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SEARCH PSR

Psilocybin and the Will to Live

Psilocybin may help suicidal patients renew their sense of meaning.

MAY 06, 2021 - BY ABIGAIL E. CALDER, MSC

TAKE PHOTO / SHUTTERSTOCK

someone's mental state after finding out they have cancer. Clinical depression can have ambiguous causes or no obvious ongoing cause at all. But these patients have learned that they may be *dying of cancer*. According to the tests, yes, they're depressed. But more accurately: they have a massive problem that might never go away again, and they are having a reasonable emotional reaction to it. An imminent and unexpectedly early death can be an intense ontological shock, leading people to question the meaning of their lives and feel demoralized, hopeless, or spiritually empty. Often patients are in considerable physical and emotional pain, and unsurprisingly, a cancer diagnosis increases someone's risk of suicide four-fold.[2] Although antidepressants may take the edge off, no pill can truly fix *that*.

But perhaps a mushroom can.

An Antidote to Despair

Back in 2016 – and several times since – psilocybin therapy made headlines for drastically and enduringly reducing symptoms of anxiety and depression in patients with life-threatening cancer.[3,4] Stephen Ross and colleagues, who conducted a 2016 trial with cancer patients at NYU, have recently returned to their data to examine how exactly psilocybin therapy influenced these patients.[2] What could possibly make a cancer patient less depressed about having cancer?

2

To find out, they focused specifically on 11 out of the original 20 patients who reported suicidal ideation prior to psilocybin therapy. These patients were suffering so badly from their cancer that they were considering ending their lives. But after a single

How Did Psilocybin Make This Happen?

It may have something to do with psychedelics' ability to create meaning.[5] During a psychedelic experience, people often have important and highly emotional insights into their lives, their problems, and what they feel to be their true values. In the words of one patient: "[The psilocybin experience] brought my beliefs to life, made them real, something tangible and true – it made my beliefs more than something to think about, really something to lean on and look forward to."[6]

Patients from psilocybin trials show that this can happen in almost infinitely many ways, with more common experiences being a diminished fear of death, re-experiencing important memories, or feelings of deep connectedness with the world.[6] Although the details differ, people who take psychedelics – whether in a trial or otherwise – often count their experiences as some of the most meaningful of their entire lives.[7–9]

ANTONIO GUILLEM / SHUTTERSTOCK

In the words of Friedrich Nietzsche, "He who has a why to live can bear almost any how."

For people who are suffering, meaning and purpose can be powerful antidotes to despair.[10] The details will vary as much as people do, but in general, someone's sense of meaning is made of their own experiences, beliefs, values, and goals, and it is something each person must find for themselves. A strong sense of one's personal purpose in life can make people resilient even when their circumstances become difficult. When people lose this, psychological well-being can die out with it. At the beginning of the trial, many of these patients reported that they *had* lost their sense of meaning. But after the psilocybin sessions, it somehow came back – and stayed, too, even at the 4.5-year follow-up.[2] This change correlated with reductions in suicidal ideation, and patients also reported that they felt less hopeless and demoralized. Perhaps the psilocybin experience helped them find their Why.

are involved in attributing meaning and significance to events in one's life.[5] A study that used LSD to enhance the meaning of music implicated areas of the pre-frontal cortex, as well as the supplementary motor area, which is involved in self-relevant processing.[5] We still have a very incomplete picture of exactly how the brain generates meaning, but however it does, psychedelics seem to send that process into overdrive in a way that is therapeutically helpful.

A drug that can help people find meaning and reduce suicidality has obvious clinical uses. Doctors and researchers have been wary about giving psychedelics to suicidal patients thus far, with good reason but mainly out of an abundance of caution.[12] Promising data on suicidality from trials like Ross et al. may allow a careful relaxation of that caution for certain patients. If psilocybin proves to be more broadly effective against suicidality, it would be the only drug apart from ketamine known to immediately and enduringly boost someone's will to live with a single dose.

And there is probably nothing special about cancer, as horrible life events go. People can lose their sense of meaning and will to live in the face of many serious health problems, traumas, and tragedies. If psychedelic therapy helps cancer patients, it may very well help others. In fact, there is already evidence that psychedelics increase the sense of meaning in diverse patient groups, as well as in healthy participants.[13] By drawing people closer to what they find meaningful in life, psychedelics may help people find their way through their worst seasons, to come out stronger and more resilient on the other side.

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2 COMMENTS Oldest

Anthony 6 days ago

Psychedelics have catalyzed a strong doubt understanding limited by physicalism/empirical method can lead to the Real, or an understanding of Truth. After all, psychedelic means "mind manifesting." Mind is not an empirical thing, it's a nonphysical, non thing, more of a phenomenon commensurate with phenomenological ontology. The brain doesn't imbue meaning, the mind does. It seems intellectually dishonest for science (neuroscience) to dismiss phantasmata and mental imagery as non existent. Which it would have to do considering there as of yet, still haven't been measured any thoughts or images in the physical thing, the brain. I seriously doubt people who… Read more »

+ -1 — Reply

Erinn Baldeschwiler 4 days ago

YES! This is a perfect encapsulation of the promise of psilocybin therapy as a means of finding purpose and meaning in one's life. The ultimate in transmutation of pain – emotional, mental and spiritual. Beautifully written (wish I had written it myself!). Thank you for this.

+ 3 — Reply

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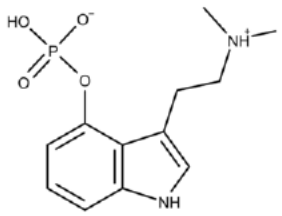

2

Psilocybin

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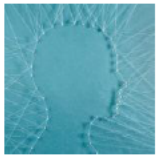

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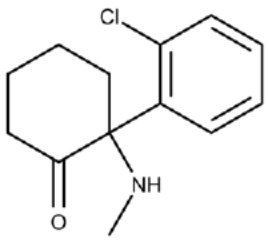

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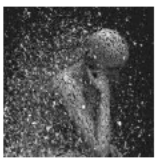

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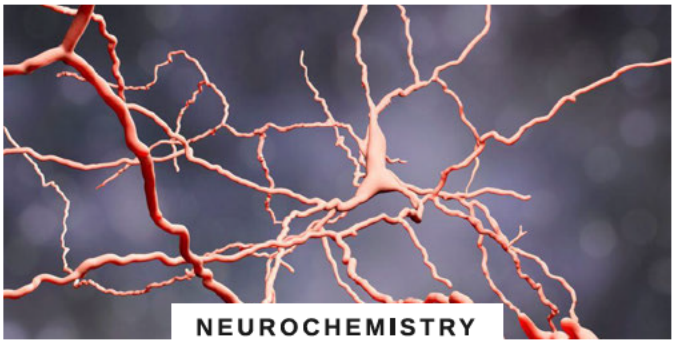

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Original Article

Defining the Roles and Research Priorities for Psychedelic-Assisted Therapies in Patients with Serious Illness: Expert Clinicians' and Investigators' Perspectives

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Abstract

Background: Recent and preprohibition studies show that patients with serious illness might benefit from psychedelic-assisted therapies for a range of symptoms, physical, psychosocial, and existential.
Objective: To explore the potential roles and research priorities of these therapies in patients with serious illness.
Design, Setting, and Participants: Qualitative study based on semistructured interviews with 17 experts in serious illness care and/or psychedelic research from the United States and Canada.
Measurements: The interview guide elicited participants' perspectives on (1) the potential roles of psychedelic-assisted therapies in this setting, (2) research priorities relevant to this population, and (3) the potential for integrating psychedelic-assisted therapies into existing delivery models of serious illness care. We used thematic analysis until thematic saturation.
Results: Domain I: Participants had polar views on the therapeutic potential of psychedelic-assisted therapies, ranging from strong beliefs in their medical utility to reluctance about their use in this patient population. They shared concerns related to the risks of adverse effects, such as delirium or worsening of psychological distress. Domain II: Research priorities primarily concerned patients with clinically diagnosed psychosocial distress, such as depression, anxiety, or demoralization. Participants also articulated potential roles extending beyond traditional medical diagnosis. Domain III: Participants emphasized essential safety and efficacy guidelines relevant to the integration of these therapies into existing models of care.
Conclusion: This qualitative study highlights issues and priorities for research on psychedelic-assisted therapies in patients with serious illness and proposes a conceptual framework for integrating these therapies into existing delivery models of serious illness care.

Keywords: hallucinogen; palliative care; psychedelic; psycho-oncology; psychosocial support systems; qualitative research; serious illness

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Introduction

Individuals living with serious medical conditions commonly experience burdensome psychological symptoms.[1,2] In this population, major depression affects 13% 29% of patients, and is associated with increased physical symptom burden, requests for hastened death, and intensity of life-prolonging treatments near the end of life.[3–8] More than 50% of patients in palliative care receive daily anxiolytics.[9,10] An increasing body of literature suggests that the spiritual or existential crisis triggered by a life-threatening diagnosis contributes to this distress.[11–13]

During the 1960s and 1970s, researchers explored the therapeutic potential of psychedelic drugs, such as lysergic acid diethylamide (LSD) and N,N-dipropyltryptamine, most often as an adjunct to psychotherapy, to reduce distress in patients with life-limiting conditions. Seven open-label studies reported improvement of physical and psychological symptoms in terminal cancer patients who were treated with psychedelic drugs.[14–19] However, the passage of the Controlled Substance Act in 1970 made these drugs illegal, and clinical research became increasingly difficult and stigmatized. Despite these hurdles, four phase 2 randomized controlled trials published between 2011 and 2016 demonstrated rapid, robust, and sustained improvements in psychological and existential distress in patients with serious illness following a single psychedelic-assisted therapy session.[20–23]

Clinicians and researchers with expertise in serious illness care play an important role in identifying and assessing novel therapeutic tools. Given the complicated history with these drugs, one may anticipate a diversity of views on these questions. If this research is going to move forward, there is a need to learn where consensus exists, and also identify and respond to possible concerns and barriers. At present, the perspectives of such experts concerning the potential clinical value and corresponding research priorities of psychedelic-assisted therapies remain unknown. To lay fundamental groundwork for future research in psychedelic-assisted therapies for persons with serious medical illnesses, we conducted key-informant interviews with expert stakeholders in oncology, psychosocial oncology, palliative care, spiritual care, and psychedelic research.

Methods

Study design, context, and oversight

We conducted semistructured qualitative interviews with leading experts in oncology, psychosocial oncology, palliative care, and psychiatry, some of them with experience in psychedelic-assisted therapy research. The Dana-Farber Cancer Institute Office for Human Subjects Research approved the study.

Participants

Eligible participants had clinical and/or research expertise related to patients with serious illness. We purposively sampled participants likely to represent a range of knowledge and perspectives about psychedelic-assisted therapy through literature review, our own professional networks, and snowball sampling (i.e., participant recommendations about others we might approach to interview). We sought the perspectives of those who had (1) researched, published academically, and/or lectured on the topic of psychedelic-assisted therapy; (2) publicly or within professional relationships expressed reservations or concerns regarding this category of interventions; or (3) demonstrated leadership or expertise in a relevant field but had not expressed an opinion on psychedelic-assisted therapy. We recruited interviewees until we reached thematic saturation, that is, when we stopped identifying additional themes or pertinent insights. Participants provided informed consent and received no compensation.

Interview guide

Y.B. (palliative care physician, research fellow) and J.S. (palliative care physician, researcher) wrote the initial semi-structured interview guide. They subsequently refined it following feedback from an interdisciplinary research team, including physicians, nurses, and psychologists, as well as test interviews with two palliative care and two psychosocial oncology providers. The final interview guide (Supplementary Data S1) elicited participants' professional experiences and their knowledge of psychedelic-assisted therapy. In addition, it explored their perspectives on the following issues: the potential role of psychedelic-assisted therapies in serious illness care, corresponding research priorities, and the integration of these interventions within delivery models of psychosocial and palliative care for seriously ill patients.

Data collection

We conducted semistructured interviews in-person or via videoconference. One author (Y.B.), who is trained and experienced in qualitative interview methods, conducted all interviews. Audio-recorded interviews lasted 13 84 minutes. We transcribed the interviews verbatim using an online automatic transcription service, double checked all transcriptions, and deidentified the document file names and content according to the study protocol.

Data analysis

With supervision from an experienced qualitative researcher (J.S.), two investigators (Y.B. and Z.S., a psychiatrist and research fellow) thematically coded interview transcripts using template analysis, an inductive and deductive approach.[24] They independently coded the first four interviews to identify themes and iteratively refined the codebook. Discrepancies were resolved through discussion with a third researcher (J.S.) until consensus was reached. Interviews were coded in Dedoose qualitative analysis software (version 8.1.10).

Results

Study sample

Seventeen of the 18 experts approached agreed to participate in the study. One declined, citing a lack of knowledge about psychedelic-assisted therapy. All were recognized experts in their respective fields, with a mean time since graduation of 33 years (range, 7 56 years). Thirteen participants worked exclusively in academic institutions, two exclusively in private practice, and two in both. All but one (retired) had a current clinical practice, and clinical responsibilities ranged

from 10% to 80% of their full-time position. Five participants were female. Fifteen were white. Mean age was 57.8 (range, 35 71). Table 1 describes participants' characteristics according to their respective fields.

Primary domains

Primary domains identified related to (1) polar views and common concerns in participants' perspectives on the potential role of psychedelic-assisted therapies for seriously ill patients, (2) potential roles and research priorities relevant to patients with serious illness, and (3) therapeutic, institutional, and societal frameworks needed to integrate psychedelic-assisted therapies into existing models of care.

Domain I: polar views and common concerns in participants' perspectives

Polar views

Participants described polar views regarding the therapeutic potential of psychedelic-assisted therapies in the care of patients with serious illness. Some believed these interventions represent a potentially powerful tool to improve quality of life, whereas others expressed strong skepticism regarding any potential therapeutic value. Table 2 highlights these contrasting perspectives according to four categories of themes: (1) participants' general attitudes; (2) how they viewed psychedelic-assisted therapies within existing therapeutic paradigms; (3) their perceptions of the clinical relevance of these therapies; and (4) their attitude toward the altered states of consciousness induced by psychedelics.

Common concerns

In addition, all interviewees highlighted the particular vulnerabilities of patients with serious illness and highlighted the need for extra caution in conducting research in this population. For example, one participant said:

> *''I think that there is a value in exploring this. But I think it has to be very circumscribed and very monitored and there need to be a lot of guardrails.''* ***P10 Psychiatrist***

We did not ask participants about their personal experiences with psychedelic drugs. However, several participants spontaneously noted ways in which their own experiences with psychedelics shaped their views on the therapeutic potential of these drugs. For example, one participant said:

> *''What I have to say from [my own experience of psychedelics] is that my view has totally changed. […] Palliative care has encouraged the idea that you should die with your ego intact. One, that it's possible and two, that it's a good thing. […]. And actually, in a way, it's quite opposite to what I've actually experienced in my psychedelic journey. […] It is really about releasing the ego and not following it, in fact.''* ***P14 Palliative care physician***

Domain II: potential roles and research priorities

Potential roles

Participants described potential roles for psychedelic-assisted therapies in the care of patients with serious illness who have clinically diagnosed psychosocial distress, such as major depressive disorder, general anxiety disorder, or demoralization syndrome. However, several also anticipated potential applications in the prevention of such conditions and in patients struggling with existential and/or interpersonal issues. For example, a palliative care physician said:

> *''Widening the scope of our thinking, I think that family dynamics and people that are having difficulty in their rela tionships with others and where there's distress, family dis tress or distress among loved ones, might be a trigger to consider someone [for psychedelic assisted therapies].''* ***P11 Palliative care physician***

Research priorities

We identified several articulated priorities for psychedelic research in seriously ill patients, including the general need for larger randomized controlled trials assessing the efficacy and safety for different indications and populations of patients. For example, one participant said:

> *''It would ultimately need a comparison with gold stan dards, a randomized controlled trial where the comparison group is getting the standard of care for serious illness.''* ***P1 Palliative care physician***

We detail in Table 3 the research priorities, potential indications, outcomes of interest, and safety parameters for psychedelic-assisted therapies as mentioned by participants.

Domain III: integration of psychedelic-assisted therapy into current practice of serious illness care

Participants considered three levels of integration of psychedelic-assisted therapies into existing practices of care for seriously ill patients: therapeutic, institutional, and societal (see illustration in Fig. 1).

Table 1. Study Sample

	Oncology	*Psychiatry psychosocial oncology*	*Palliative care*	*Spiritual care*	*Psychedelic-assisted therapy research*
No of respondents	3	4	4	3	3
No of females	1	1	2	0	1
Years since graduation, mean (sample range)	26.6 (22 35)	30.25 (17 42)	22.5 (7 33)	43 (39 49)	44.3 (37 56)
Percentage of time spent on clinical duties, mean (sample range)	41.6 (20 80)	25 (10 30)	30 (20 50)	32.5 (25 40)[a]	33.3 (20 50)

[a]Mean on two participants as one was retired.

Table 2. Polarities and Common Concerns in Participants' Perspectives on Psychedelic-Assisted Therapies in Seriously Ill Patients

Themes	*Subthemes*	*Opposite subthemes*
Category 1: General attitude		
Level of openness	***Closed***	***Open***
	Honestly, my first reaction is I'm a very anti-drug-and-alcohol human outside of being a physician. And so, my reaction comes from that. ***P13 Oncologist***	*I think it's very interesting and I'm all for doing the research. […] There's a group of people who are going to die, immediately or eventually, and they're trying as best as they can to make meaning out of their situation and come to terms with it. And anything that helps them, I think would be a huge benefit.* ***P15 Psychiatrist***
Level of enthusiasm	***Reluctant***	***Enthusiastic***
	If it was a medicine that could be easily prescribed and easily taken, that would feel different to me than something that is harder to take and more complicated to procure. And it just seems like a lot of effort would need to go into this area for something that would probably have a marginal impact if any on the care patients. ***P6 Psychiatrist***	*I would say I've felt like this is an amazing tool for us to learn more about and explore. I am enthusiastic about it.* ***P11 Palliative care physician***
Familiarity with psychedelic-assisted therapy	***Unfamiliar***	***Familiar***
	I've not read any data. So, I don't have any basis to form an opinion. If there's data out there I've not reviewed it. ***P13 Oncologist***	*We were very impressed with the treatment outcomes for our research subjects. There was a noticeable drop in their anxiety, improvement of mood, lessening in their demoralization, improved overall quality of life. There was no question in our mind that this experience had value for the research subjects who participated.* ***P5 Psychiatrist***
Category 2: Therapeutic paradigm		
Lens through which psychedelic-assisted therapy is regarded	***Scientific***	***Spiritual***
	I think in general I'm sort of cautiously optimistic about the promise of these treatments. But I think right now it's still a promise and I don't think there are enough data that have been rigorously collected where I'd be comfortable using this on my patients. And I think, going forward, that for our field of palliative care and for serious illness care in general, it's very important for us to do these studies in the most rigorous way and under very controlled conditions. At least at first, so that we really understand what we're doing. ***P1 Palliative care physician***	*Helping people with [existential distress], what tools do I have?* *I have a charming and fairly clever chaplain[…]. We do clever things, we do dignity therapy, we do legacy work, we explore and create a relational container for them. And yet still 30 to 40 percent of people are in grave, grave existential distress because of the trauma informed life history that they bring, because of their conflicted relationships, because all of the dark and difficult things.* *And yet I think we cheat them out of an available and powerful safe mystical experience.* ***P7 Palliative care physician***
Uniqueness of psychedelic-assisted therapy in the modern medicine paradigm	***Comparable to any psychosocial and palliative care intervention***	***Unique intervention model***
	I think it would just be one of the other tools that's used. Some people have pain, some people have shortness of breath, but as you see that existential distress is a big problem for someone, then you would refer them to that therapy. ***P4 Oncologist***	*We are talking about a reaction to treatment that is not typical of anything that we've used before, which alters mental state and mood and cognition in ways that traditional treatments, even psychosocial treatments don't. It sounds akin to what people experience as a variety of religious experience.* ***P15 Psychiatrist***
Lens through which psychological and existential issues in seriously ill patients are regarded	***Treating pathology (illness)***	***Achieving wholeness (health)***
	As we already have treatments that are efficacious for psychological distress and existential distress at the end of life, I'm not sure it's necessary to use substances to do something similar. ***P6 Psychiatrist***	*Things like helping someone find a way to die with some sense of meaning, coherence to their lives a sense of a minimal amount of existential guilt, accepting the life that they've lived, finding some way to face that with some sense of peace and equanimity is part of the whole… a holistic care of a patient at the end of life. It is as important as treating their pain.* ***P9 Psychiatrist***

(*continued*)

TABLE 2. (CONTINUED)

Themes	*Subthemes*	*Opposite subthemes*
Category 3: Relevance		
General therapeutic value	***Futile***	***Highly significant***
	So, to me it seems like a very risky treatment… a very risky treatment, with relatively low benefit for a very small number of patients. […] And so, there is a part of me that just sort of wonders about the whole enterprise of doing this kind of work. ***P10 Psychiatrist***	*There's a huge gap, which you face every day as an oncologist, which is trying to help patients cope with anxiety and stress that go with having a cancer diagnosis. And deal with their mortality. And really seeing that every day, and yet having limited tools that really help them. Whether it's referring to a social worker or a psychologist, or antidepressants, you feel like you don't really get to the heart of it. It feels like this has a potential to really, to get to the heart of something that's really difficult for us to address. Right now, we don't have any tools for it. So, there seems to be a promise that these tools could maybe address that.* ***P4 Oncologist***
		What would the world be like if a significant number of people really no longer feared death? ***P3 Psychologist***
Relevance to patients	***For a selected few patients***	***For the majority of seriously ill patients***
	I think it's a minority of patients that need it or would want it. ***P12 Psychiatrist***	*I think [existential distress in seriously ill patients] is very frequent. The question is how high it is and what's the threshold to refer someone [to psychedelic-assisted therapy]. I have not met many patients with advanced cancer that don't have some degree of existential distress. I mean most humans struggle with mortality.* ***P4 Oncologist***
Anticipated patient's perspectives	***Reluctance***	***Adherence***
	When you start talking about LSD and mushrooms, I imagine that you have a higher hill to climb to convince patients. Except those that are already amenable to those things. So, I think that's the other piece to figure out is explaining to patients why this schedule-1 illegal drug is something they should try. […] we could all say it's great and then we can't find a single patient to agree. ***P12 Psychiatrist***	*It's more like just educating them on the safety and the studies that show efficacy. You know, when I've talked to patients about it, even now, it's more of a novelty and there's a shock initially, but then, it quickly moves into that science and most patients are desperate to get help.* ***P4 Oncologist***
Relevance to providers	***Not needed***	***Needed***
	As we already have treatments that are efficacious for psychological distress and existential distress at the end of life, I'm not sure it's necessary to use substances to do something similar. ***P6 Psychiatrist***	*The treatments that we have for mental health are shitty. We have shitty treatments for depression. Patients reject them because they don't work well. And I think that the medical community has not really come to terms with the fact that a huge number of patients basically reject SSRIs and psychotherapy, for good and not good reasons. But they don't want them. And how is it going to help them for us to say you've got to try these first. I guess I'm not clear about that, given that neither of them works that well.* ***P14 Palliative care physician***
Category 4: Effect on patients		
Perception of psychedelic-assisted therapy safety	***Unsafe***	***Safe***
	I think it's very risky to take a fragile, a terminally ill patient and give them a hallucinogen. I think it's frightening to me, frankly. The potential adverse effects, I think, are great for them. ***P9 Psychiatrist***	*I don't have so much worries [about using PAT in seriously ill patients]. I mean they don't really have any addictive potential and it's hard to overdose on them. So physiologically they're pretty safe. And you know it appears at least from the studies and experience that we have that there doesn't seem to be a lot of adverse events.* ***P4 Oncologist***

(*continued*)

Table 2. (Continued)

Themes	*Subthemes*	*Opposite subthemes*
Subjective experience of the effect	***Distressing*** *My concern is: you give a patient a hallucinogenic drug, they have frightening hallucinations, right? and is extremely distressing for them. Why would I want to put a patient through that? It's as distressing as having pain!* ***P9 Psychiatrist***	***Relieving*** *It's a dimension of human consciousness that feels intrinsically self-validating, beautiful, meaningful. […] It's a world beyond time and space and substance, where there is a sense that 'all is well'. And when people approach that state consciousness it's often described as a sort of homecoming.* ***P3 Psychologist***
Perception of the psychedelic effect	***Getting high*** *I think the people who are going to be most interested in this are people who have a prior psychedelic and/or other drug experience. The question is sort of what did they gain from it? […] Is it just more of the same 'I 'd like to be high'. You know, I enjoy that experience. Or is there something that is sort of beneficial for their coping with their illness other than having a nice few hours experience.* ***P10 Psychiatrist***	***Accessing a mental state catalyzing psychotherapy and healing*** *It is several hours of time where there is a tremendous opportunity to do some healing work, to do some deep valuable effective psychotherapy.* ***P5 Psychiatrist***
Impact on patient's decision making	***Compromising*** *A psychedelic experience gives rise to a certain set of inner experiences and ideas and feelings. The question is: are those the ones that are going to be most beneficial for the patient to focus on in their last stage of life? Is it going to make things better for them and their families? And maybe yes… and maybe no. And because the energy is so limited during that phase of life, if you're focusing on one thing, you're not focusing on something else.* ***P10 Psychiatrist***	***Empowering*** *Quite often really the person who has the psychedelic experience, if it's positive, becomes sort of the social worker for the family. That does wonderful things of empowering the dying person, you know, that ''I still have an important role in this family.'' You know, ''I've got to prepare these people for my death.''* ***P3 Psychologist***

LSD, lysergic acid diethylamide; PAT, psychedelic assisted therapies; SSRI, selective serotonin reuptake inhibitors.

At the therapeutic level, considerations included the following: (1) preparation, the drug-assisted therapy session, and follow-up as integral parts of the therapeutic model; (2) therapeutic alliance and boundaries as crucial aspects of the relationship between the patient and the therapist; and (3) therapeutic education of patients, family caregivers, and other care providers. At the institutional level, participants described the importance of ensuring appropriate physical settings for the psychedelic-assisted therapy session, involving interdisciplinary teams, and defining requirements for training and certifying therapists. Finally, societal level themes focused on the regulations and financial structures needed to guarantee high-quality research, access, accountability, and equity. Table 4 provides illustrative quotations for each of these subthemes.

Discussion

We interviewed 17 experts involved in the care of patients with serious illness. We solicited their perspectives on the potential roles of psychedelic-assisted therapies, research priorities relevant to this population, and the potential for integrating psychedelic-assisted therapies into existing delivery models of serious illness care.

We found polar views regarding the use of psychedelic-assisted therapies and shared recognition of the need for caution. Several participants expressed skepticism, questioning the relevance and the safety of this approach and citing seriously ill patients' vulnerability to side effects, such as delirium or intervention-related distress. In addition, some could not reconcile the association of psychedelics as drugs of abuse with the idea of psychedelics as therapeutic tools.

While recognizing the same reservations, other participants expressed enthusiasm for further studies of psychedelic-assisted therapies. Three themes characterized the views of those with strong interest in pursuing research: perceived unmet clinical needs in individuals with serious illness; limitations of existing interventions; and the potential rapid action of psychedelic-assisted therapies in reducing distress associated with a life-threatening disease.

We identified research priorities in two overarching domains. First, participants called for detailed therapeutic protocols that specify which patients are eligible to be treated, when such treatments are initiated, in what settings, with which particular psychedelic, and at what dose. Second, participants highlighted the importance of research protocols that address critical questions about mechanism of action and efficacy of these therapies. Participants described potential indications, outcomes of interest, as well as safety parameters to consider in designing clinical trials.

Finally, when asked about how to integrate psychedelic-assisted therapies into existing models of clinical care, categorical responses referred to therapeutic, institutional, and societal determinants of safety, efficacy, and inclusiveness.

Table 3. Research Priorities, Potential Indications, Outcomes of Interest, and Safety Parameters for Psychedelic-Assisted Therapies in Seriously Ill Patients

Research priorities	
Building research protocols	**Quote examples**
Indications Patients Efficacy Mechanism of action Safety Impact on a health care system level	*In the first place you want to see if it's effective, for whom it is useful, and then you want to see what the essential contributing therapeutic factors are.* ***P17 Psychiatrist*** *I'm curious about whether it only is so dramatic in people that are feeling really intense distress or whether it can be an adjunct to treatment for a lot of patients.* P11 Palliative care physician
Defining therapeutic protocols	**Quote examples**
Amount of therapy Number of therapists Group therapies Dosage Drug Type of psychotherapy provided	*We're just in the infancy of learning all that: whether a group therapy is better than an individual and what the optimum dosing is, the number of sessions,* etc. ***P4 Oncologist*** *One question is what psychotherapy people would have in association with [psychedelic-assisted therapy].* ***P10 Psychiatrist***
Potential indications	
Anxiety Depression Existential distress Demoralization Hopelessness Adjustment disorder Pain	Prevention of these conditions
Outcomes of interest	
Patients' benefits	Physical symptoms Pain/pain medication Dyspnea Mood Anxiety Meaning Existential/spiritual well-being Coping/resilience Life priorities/personalized outcomes Quality of life Survival
Relatives' benefits	Quality of life of relatives Bereavement
Communication/interpersonal relationships	With loved ones With care providers
Decision making	Serious conversation/goals-of-care discussions End-of-life decisions Patient engagement with treatment
Care providers' benefits	Meaning at work Burnout
System benefits	Service utilizations at end of life Cost
Safety parameters	
Populations of patients more at risk of adverse effect	Brain tumor or metastasis Patients with psychosis or family history of psychosis Older adults Severe heart disease Critically ill patients
Monitoring potential psychosomatic risks	Cardiotoxicity Seizure Delirium Behavioral issues, accidents Lasting neuropsychiatric toxicity Distressing/(re)traumatizing impact of the subjective experience induced by psychedelic-assisted therapy

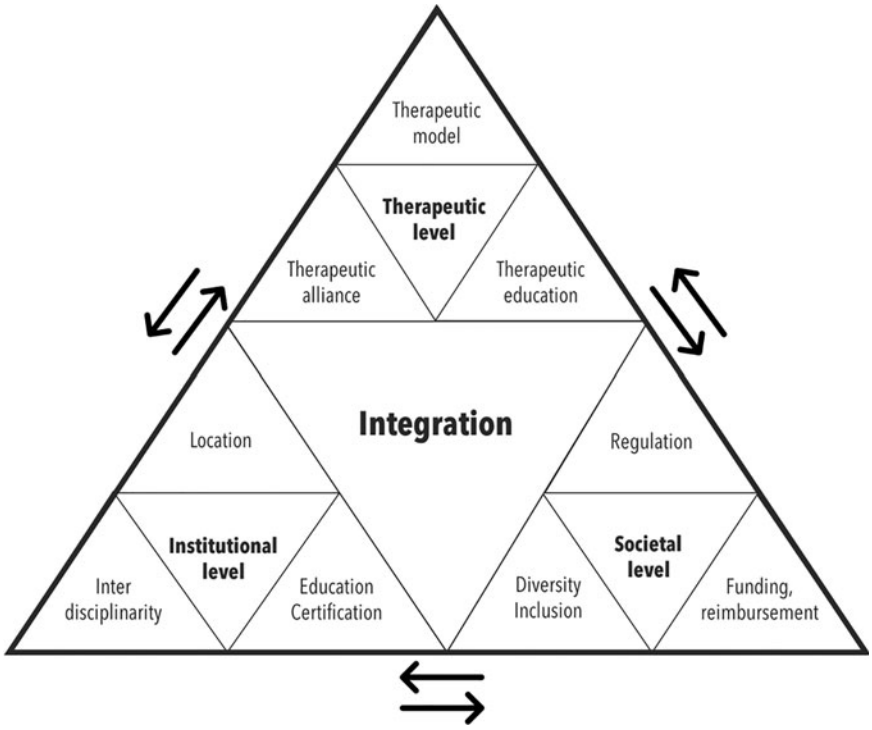

FIG. 1. A multifaceted model for the integration of psychedelic-assisted therapies into existing models of serious illness care.

Using this matrix, we developed a conceptual framework reflecting participants' guidelines for such an integration.

Research need

Polarized views observed in this study are consistent with findings of a recent survey based on a convenient sample of 324 American psychiatrists, in which a quarter of respondents considered psychedelics unsafe, even under medical control, while 42.5% viewed this class of drugs as promising for the treatment of psychiatric disorders.[25] Factors influencing those views remain unknown. However, our findings suggest that openness to researching these therapies in seriously ill patients may be influenced by the following: (1) the perception of unmet needs and persistent psychosocial and existential distress in this population; (2) professionals' knowledge about empirical studies of psychedelic-assisted therapies; and (3) prior personal experience of altered states of consciousness whether or not induced by psychedelics.

Nearly two decades of research link early assessment and treatment of physical and psychosocial symptoms in patients with advanced cancer with improved quality of life, mood, and spiritual well-being.[26,27] Similarly, seriously ill patients' quality of life and end-of-life care both benefit from spiritual assessment and care.[28,29] Psychotherapeutic interventions focusing on acceptance, dignity, and meaning such as Meaning-Centered Psychotherapy, Dignity therapy, or Managing Cancer And Living Meaningfully (CALM) have shown promising reductions in end-of-life distress.[30–32] Nevertheless, psychosocial and existential distress remains largely underaddressed in seriously ill patients, undermining health care outcomes.[28,33]

It remains to be determined whether, to what extent, and for which populations, psychedelic-assisted therapies can improve psychosocial and existential outcomes in seriously ill patients. Despite studies in controlled settings that have found few adverse events following psychedelic-assisted sessions in both healthy volunteers and seriously ill patients, safety of psychedelic-assisted therapies in medically frail patients cannot be guaranteed.[20–23,34] For most of the interviewees, further research was needed to address these questions.

Publications by oncologists, psychiatrists, palliative care physicians, and psychedelic researchers have underscored the need to further study the benefits and risks of psychedelic-assisted therapies in people with serious illness.[35–41] Similarly, in Barnett's 2018 survey, 80.5% of responding psychiatrists believed that psychedelics deserved further research for treatment of psychiatric disorders.[25]

Therapeutic models in serious illness care

Results of our study highlight a need to test standardized protocols of psychedelic-assisted therapies to better understand clinical benefits and underlying mechanisms of action of these treatments. Several clinical and nonclinical models have informed therapeutic protocols for psychedelic therapy in patients with distress related to a life-threatening condition. These include sacred healing rituals of indigenous people that may involve peyote, ayahuasca, or hallucinogenic mushrooms; early psycholytic and psychedelic treatment models based on transpersonal and humanistic psychology; and psychotherapeutic approaches to existential distress in patients confronted with life-threatening illnesses.[42]

Psychedelic-assisted therapy protocols being studied include the following: (1) the psilocybin mystical experience model that is used in patients with advanced cancer or alcohol use disorder[20,22,23]; (2) methylenedioxymethamphetamine (MDMA)-assisted therapy for individuals with post-traumatic stress disorder (PTSD) or autism spectrum disorder with social

Table 4. Integration of Psychedelic-Assisted Therapies into Exiting Models of Serious Illness Care

Themes	*Quote examples*
Therapeutic level	
Therapeutic model: preparation, drug session, and follow-up	*We know from the early days of psychedelic research that […] it's not only ineffective, but I would say unethical to 'simply' give a psychedelic to someone. That it always has to be in the context of establishing a trusting relationship, some instruction on how to navigate in these inner worlds and a few hours of reflection on what they experienced and how to relate that to their everyday life and relationships. [Psychedelic-assisted therapy] will always need to include these three components of preparation, the actual administration of the substance and the integration as a package.* ***P3 Psychologist***
Therapeutic alliance and boundaries	*Psychedelics temporarily lower defenses. During several hours of time, there is a tremendous opportunity for healing work, for deep valuable effective psychotherapy. But individuals are more vulnerable, more open and more likely to be impacted by the world around them and external interventions. It is essential that very strong ethical standards be established and maintained […].****P5 Psychiatrist***
Therapeutic education	*It's important to educate [patients] on the safety and efficacy of the studies. When I've talked to patients about it, even now, it's more of a novelty and there's a shock initially but then, it quickly moves into that science and most patients are desperate to get help. So, it's not usually a big deal to educate them.* ***P4 Oncologist***
Institutional level	
Setting, location of psychedelic-assisted therapy	*The settings may be cancer centers but also, I would think, hospices.* ***P12 Psychiatrist***
Interdisciplinarity, articulation with other specialized and supportive care	*Palliative care is a team game. I would want [a physician, a chaplain] and a social worker who know [the patient] and have assessed theirspirituality and religion, their markers, their whatever the science of it is, sit together and say that this patient might benefit from a trial of this psychedelic.* ***P8 Chaplain***
Training, education of population, providers, and other health care professionals	*[Therapists from] backgrounds in the psychiatric nursing or psychology, or psychiatry or social work or pastoral counseling, specially trained as psychedelic therapists, hired by a palliative care division […]. There are some things you need to know to teach people how to benefit maximally from the opportunity and to ensure safety and efficacy. You can't just give the drug. But those are learnable.* ***P3 Psychologist***
Societal level	
Regulation	*At this point […] we know they're safe and there a lot of signals saying that it's helpful. So, I think the more meaningful studies now have tolead to regulatory approval […] to get access to it.* ***P4 Oncologist***
Funding, reimbursement	*If Medicare is going to start covering this, it can't be a luxury treatment that costs a fortune. So, what's the minimum that you can offer that provides basic safety and efficacy?* ***P3 Psychologist***
Diversity and inclusion	*The research and therapeutic models need to find a way to acknowledge the debt that is owed to the underground therapists who've been keeping this practice alive for all these years of sort of 'the Dark Ages'. And also, to indigenous people. There has to be some overt acknowledgement of that.* ***P2 Nurse***

anxiety[43,44]; and (3) psilocybin-assisted group therapy for long-term HIV survivors with demoralization.[45] Integration of psychedelic-therapies within behavioral therapies, such as acceptance and commitment therapy and mindfulness-based cognitive therapy, is being developed.[46,47] Translational research is needed to link findings from neurobiology and neural imagery with clinical efficacy and potential therapeutic applications.[48,49]

The literature reinforces specific challenges identified by our participants related to palliative care and psychedelic research, respectively. First, seriously ill patients often present with physical and cognitive limitations that restrict the types of studies and research methods that are feasible or ethically acceptable.[50,51] Second, double-blinded controlled studies of psychedelic therapies are impractical due to the nature of psychedelic experience.[52] These challenges warrant concerted pragmatic interdisciplinary research strategies.

Integration into existing models of serious illness care

Participants considered three levels of integration of psychedelic-assisted therapies into existing models of care and health service delivery. At the *therapeutic level*, guidelines from early and more recent psychedelic research highlight two major parameters of safety and efficacy.[42,53–55] First, screening should identify patients at increased risk of adverse events. Second, support and monitoring of patients through preparation, the drug-assisted therapy session(s), and during follow-up must attend to the physical, psychological, social, and spiritual dimensions of care. This is highlighted by a recent report of long-term adverse reactions following LSD treatments conducted in the 1960s in patients with psychiatric conditions who were treated without psychotherapeutic support.[56]

At the *institutional level*, efforts to study and integrate psychedelic-assisted therapies in clinical research are increasing. The Multidisciplinary Association for Psychedelic Studies (MAPS), founded in 1986, has championed research and regulatory advocacy.[57,58] Since 2016, the Certificate Program in Psychedelic Therapies and Research of the California Institute of Integral Studies has trained 241 health care and spiritual care professionals to conduct psychedelic-assisted therapy within research.[53,59] The Imperial College of London established the Center for Psychedelic Research in April 2019.[60–62]

At the *societal level*, researchers have emphasized the need to adapt existing systems of drug control to facilitate clinical studies of psychedelic-assisted therapies, while minimizing the risk of misuse.[52,58,63] This need is timely. Since 2018, the FDA granted breakthrough therapy status for MDMA-assisted psychotherapy in PTSD and psilocybin-assisted therapy in treatment-resistant depression and major depressive disorder. Other researchers have emphasized the need and opportunity of including indigenous populations and ethnic minorities in psychedelic studies.[64]

The multiple layers of integration provide context for research paradigms, protocols, and priorities. Our findings suggest that the development of a consensus-driven agenda, which prioritizes key questions and clinical situations, represents a critical next step in psychedelic research. We anticipate that such an effort would enhance a federally funded research program.

Limitations

Some limitations of this study deserve attention. First, our findings distill views of leading experts in pertinent fields but may not represent the majority views of health care providers. The majority of participants comprised white male physicians whose clinical work has focused on oncology patients. Although we reached thematic saturation, a larger and more diverse study sample might have resulted in different findings. Population-based surveys are needed to address these limitations and to analyze how demographic and other factors influence these views. Second, although we recruited some participants who were unfamiliar, skeptical, and/or disapproving, the resulting sample included more proponents than skeptics of psychedelic-assisted therapies. Third, we did not ask participants about personal experiences with psychedelic drugs, yet several spontaneously mentioned that their own experience or inexperience with psychedelics shaped their views on their therapeutic potential. Prior personal experience, positive or negative, may have influenced these views and should be explored in further studies.

Conclusion

This qualitative study suggests research opportunities and priorities relevant to the emergent field of psychedelic-assisted therapies for those with serious illness. Our analysis of expert clinicians' and researchers' perspectives identified several considerations to guide high-quality research. Key stakeholders should engage in a multidisciplinary consensus-building process to define a research agenda for psychedelic-assisted therapies within the care of individuals with serious medical illnesses.

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Supplementary Material

Supplementary Data S1

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Psilocybin Revisited: The Science Behind the Drug and Its Surprising Therapeutic Potential

March 9, 2021
Michael W. Jann, PharmD, FCP
Psychiatric Times, Vol 38, Issue 3, Volume 03,

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Psilocybin and psilocin are the main psychedelic agents of the psychoactive mushroom genus Psilocybe.[1] Historical and cultural use of these psychoactive mushrooms dates back 3000 years in Mexico and the Southwestern regional areas of the present-day United States. Scientifically, psilocybin was isolated and identified in 1958, synthesized in 1959, and used in various experimental research studies in the early 1960s. During that time, psilocybin and other psychedelic agents such as lysergic acid diethylamide (LSD) generated considerable controversy. Outside of recreational use, could they be used safely as therapeutic interventions?

The pharmaceutical company Sandoz ceased LSD and psilocybin manufacturing in 1965, and in 1970, the Controlled Substances Act placed psilocybin, LSD, and other psychedelic drugs under the Schedule I designation.[1,2] This action resulted in a cessation of research associated with these agents. The revival of research into psilocybin and LSD began 25 years later under strict restrictions, when preliminary findings displayed promising results for a variety of psychiatric disorders. In the past several years, there have been more research studies on psychedelics than at any previous time.

The FDA approved the psychedelic agent, esketamine nasal spray for treatment-resistant depression (TRD) in 2019; this opened the door to the novel therapeutic approaches of psychedelic agents. In 2018, the FDA designated psilocybin for TRD and 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder (PTSD) as breakthrough therapies.[3] Based on these recent studies and approvals, psilocybin may have a growing role in the treatment of TRD and other psychiatric disorders.

Psilocybin reportedly has a low abuse potential and yields no physical dependence, based on the 8 factors of the Controlled Substances Act. It was recommended to be rescheduled as a Controlled Substance Schedule IV drug with a risk evaluation mitigation strategy (REMS) if approved by the regulatory agencies.[4,5]

Pharmacology

The structures of psilocybin (O-phosphoryl-4-hydroxy-N,N-dimethyltryptamine) and its active metabolite psilocin (4-hydroxy-N,N-dimethyltryptamine) are shown in the **Figure**, and they bothbelong to the group of tryptamine/indolamine hallucinogens that are related to serotonin.[1,6] Psilocybin can be considered a prodrug, as it is rapidly converted to psilocin in the gastrointestinal (GI) tract by alkaline phosphatase and nonspecific esterases, where 1.0 mol of psilocin is equal to 1.4 mol of psilocybin.[1] Psilocin is the active molecule that produces the pharmacologic effects of a selective agonist of serotonin (5-HT) receptors, which include 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2B}, and 5-HT_{2C} receptor subtypes.[1,7] Compared to other similar 4-OH substituted tryptamines, psilocin has the most potent binding affinity (Ki) for 5-HT_{2A} receptors (6.0 nM), 5-HT_{2C} receptors (10 nM), and to a lesser extent, 5-HT_{2B} receptors (410 nM).[1,8]

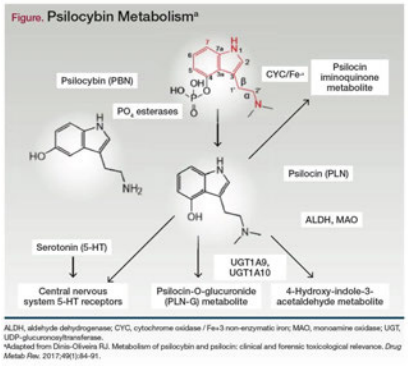

Figure. Psilocybin Metabolism[a]

Preclinical studies have shown that 5-HT_{2A} receptor activation in the cortical and subcortical structures is the unifying mechanism by which psychedelics exert their hallucinogenic and other assorted psychological actions.[7] Depending upon the dose used, the specific psychedelic agent, and possibly, the 5-HT_{2A} receptor density in the different neuronal areas, psilocybin and other psychedelic agents can exert different modulatory actions across the various cortical regions. The administration of ketanserin (a 5-HT_{2A} receptor antagonist) in human clinical studies attenuated the psychological effects of psilocybin, psilocin, and LSD.[7] The role of 5-HT_{1A} receptors in human psilocybin studies remain to be elucidated.

Besides 5-HT receptors, psychedelic agents may possess other pharmacologic actions that contribute to their behavioral and psychological effects. LSD was reported to interact with considerable affinity at the dopamine receptor with stereospecificity, as d-LSD was 1000 times more potent than l-LSD.[9] A positron emission tomography (PET) study examined the use of psilocybin in healthy volunteers (N = 7) and its effects on in vivo D2 receptor binding using 11C-raclopride in the striatum. Dosed at 0.25 mg/kg orally, psilocybin produced changes in mood, thinking disturbances, illusions, and visual hallucinations.[10] Psilocybin also significantly decreased 11C-raclopride binding potential bilaterally in the caudate nucleus (19%) and putamen (20%), which was consistent with a reciprocal increase in endogenous dopamine. These findings indicate that 5-HT_{2A} receptor activation can be a factor for modulating striatal dopamine release in acute psychosis. Psilocybin may be a useful pharmacologic agent for examining the complex interactions between serotonin-dopamine systems and various psychiatric conditions, such as schizophrenia.

The activation of 5-HT_{2A} postsynaptic receptors by psilocybin is also believed to increase glutamate release by the subsequent activation of postsynaptic α-amino-٣-hydroxy-٥-methyl-٤-isoxazole propionic acid (AMPA) receptors.[7] The prefrontal cortex (PFC) and other cortical areas that highly express 5-HT_{2A} receptors receive excitatory glutamatergic input from thalamic projections, but also send output to both the cortical and thalamic regions. The activation of presynaptic 5-HT_{2A} receptors in the thalamocortical afferents contributes to the psychedelic-induced modulation of glutamatergic transmission to the PFC. Thus, these dual actions from the presynaptic

and postsynaptic 5-HT_{2A} receptors form a cyclic feedback process for 5-HT_{2A} receptor activation of glutamate effects in the central nervous system, leading to a complex cortical-thalamic neurocircuitry.[7]

Pharmacokinetics

Psilocybin is rapidly converted to the active molecule, psilocin. Specific bioanalytical assay methods have been developed to quantify psilocin, to determine its pharmacokinetic (PK) profile. An early study with psilocybin was conducted in healthy volunteers (N = 7), in which each participant received an intravenous (IV) dose of 1 mg and an oral dose of 0.224 mg/kg (range 10 to 20 mg).[11] The estimated mean oral bioavailability of psilocin was 52.7% ± 20%. The following mean PK parameters reported from the oral route were the time to maximum effect/concentration (T_{max}) of 105 ± 37 min; peak plasma concentration (C_{max}) of 8.2 ± 2.8 ng/mL; and elimination half-life ($T_{1/2\beta}$) of 163.3 ± 63.5 min. An almost immediate phosphorylation of psilocybin takes place, and results from the IV administration noted a mean psilocin T_{max} of 1.9 ± 1.0 min; C_{max} of 12.9 ± 5.6 ng/mL; and $T_{1/2\beta}$ of 74.1 ± 19.6 min. The psychological effects reportedly began at 20 to 90 min, and within 2 min from the oral and intravenous routes, respectively.

The major psilocin metabolite formed via glucuronidation is psilocin glucuronide (psilocin-G), as shown in the **Figure**.[6] Psilocin-G is primarily eliminated from the body by renal excretion. The amount of psilocin-G produced was determined in another healthy volunteer (N = 8) PK study, by giving a single oral dose of psilocybin 10 to 18 mg (mean 14 ± 3 mg), and urine samples were collected over the following 24 hours.[12] The mean psilocin $T_{1/2\beta}$ was 3.3 ± 0.6 hours (closely resembling the previous study[11]) with the additional findings of a mean free psilocin amount of 3.4% ± 0.9% and mean psilocin-G excretion of 60.6% ± 27.1%, supporting the renal pathway as the primary elimination route.

In a population PK study, healthy volunteers (N = 12) were given escalating single oral doses of psilocybin at 0.3, 0.45, and 0.6 mg/kg, with a minimum of a 4-week interval between dosage administrations.[13] The final model developed from the PK analysis was a single compartment model with linear absorption and clearance. The median area under the concentration-time curve (AUC) for psilocin was linear at 140 mg-hr/L, 213 mg-hr/L, and 267 mg-hr/L, corresponding to the doses of 0.3 mg/kg, 0.45 mg/kg, and 0.6 mg/kg, respectively.

Once psilocin is formed, it is mainly metabolized to psilocin-G (90%), and a small portion is converted to psilocin (10%). This can partially explain the interpatient variability observed with psilocybin administration. The study reported only 1.7% of the psilocybin dose found as psilocin in the urine, with a calculated psilocin renal clearance of 1 mL/min/kg, which corresponds to 58% of the creatinine clearance.[13] These findings suggest that psilocybin dosage reductions are not necessary in patients with mild to moderate renal impairment.

The metabolic profile of psilocybin is presented in the **Figure**. It shows that after conversion to psilocin, several metabolic routes are possible. As noted, psilocin-G is the major pathway (bold arrow line) with 2 minor pathways.[1,6] Psilocin-G formation occurs via phase 2 metabolism with hepatic uridine 5′-diphospho (UDP)-glucuronosyltransferase (UGT) 1A9 and the small intestine UGT1A10.

In the second minor pathway, psilocin can be metabolized to 4-hydroxy-indole-3-acetaldehyde by 2 enzymes: aldehyde dehydrogenase (ALDH) and monoamine oxidase (MAO). It should be noted that alcohol and MAO inhibitors such as phenelzine may suggest interesting questions regarding potential drug-drug interactions that can lead to pharmacokinetic and/or pharmacodynamic effects. The metabolite, 4-hydroxy-indole-3-acetaldehyde is then further converted to 4-hydroxyindole-3-acetic acid and 4-hydroxytryptophole.[14]

The third minor metabolic pathway for psilocin takes place via the cytochrome oxidase enzymes (it is unknown whether this is related to the cytochrome P450 oxidase enzymes) and non-enzymatic Fe3+ to form psiloc[x].minoquinone.[6]

Clinical Drug Development

Earlier PK studies established the initial parameters for psilocybin dosing and provided information on the onset of its psychological effects for drug and product development. The next steps are to correlate the psilocybin (psilocin) clinical PK effects with its pharmacodynamics. A PET study conducted on healthy volunteers (N = 8) who were given oral psilocybin (doses ranging from 3 mg to 30 mg) evaluated plasma psilocin concentrations, while assessing 5-HT_{2A} receptor occupancy.[15] Participants self-assessed their intensity ratings for clinical effects using a Likert scale from 1 to 10 (1 = least intense and 10 = most intense). Plasma psilocin C_{max} values displayed a linear correlation with doses of 3 mg to 30 mg (2.3 mg/L to 19.3 mg/L, respectively). The 5-HT_{2A} receptor occupancy (%) results displayed a sigmoidal relationship with doses of 3 mg (42.9%), 15 mg (63.2%), and 30 mg (65.2%). Investigators observed a wide interpatient variability in psilocin plasma concentrations. Generally, the intensity ratings > 5 occurred when receptor occupancy approached 60% and psilocin plasma concentrations > 7.5 ng/mL.

A phase 1 clinical trial with the psilocybin formulation COMP360 was conducted in healthy volunteers (N = 89), in which participants randomly received a single 10 mg or 25 mg dose of psilocybin or placebo.[16] The study aimed to evaluate the emotional and cognitive responses of participants, along with the safety and tolerability under strict procedures. The study found that psilocybin was well tolerated, and mood alteration was the most frequently reported effect. The most notable adverse effects were hallucinations and illusions, with a slightly higher incidence in the 25 mg dose than the 10 mg dose. These adverse effects occurred in about 67% of the subjects on day 0 of drug dosing and were resolved with cessation of any remaining adverse effects by the next day. No significant changes were observed in vital signs.

These findings showed that COMP360 was well tolerated and the psychological effects were transient and consistent with those observed in previous studies. Although significant changes in vital signs were not found,[16] prior studies reported the following adverse effects with psilocybin 8 to 12 mg: mydriasis, change in heart rate, hypotension or hypertension, nausea, reflex tendencies, and tremors.[14] Furthermore, if participants experienced significant hallucinations, illusions, or other psychotic symptoms, treatment with second-generation antipsychotic agents, such as risperidone or olanzapine, was suggested.[1,17] Haloperidol was reported to alleviate only the euphoric, depersonalization, or derealization effects and not the visual hallucinations.[1] It would be interesting to deduce the actions of pimavanserin, an antagonist of 5-HT_{2A} and 5-HT_{2C} receptors. Pimavanserin is FDA-approved for Parkinson disease psychosis, for which hallucinations (visual and auditory predominantly) and illusions occur.[18]

Treatment-Resistant Depression

Esketamine is a noncompetitive N-methyl D-aspartate (NMDA) receptor antagonist that is FDA-approved for treatment-resistant depression (TRD). Esketamine underwent a phase 2 proof-of-concept study and then proceeded to the phase 3 clinical trials.[18-20] TRD was defined as a failure to adequately respond to 2 different antidepressants.

Esketamine is administered twice weekly at doses of 56 mg or 84 mg. Each clinical trial had treatment groups administered placebo nasal spray plus an oral antidepressant or esketamine nasal spray plus an oral antidepressant. Therefore, each patient continued to receive treatment with an antidepressant as the standard of care. From a safety perspective, esketamine was well tolerated. However, the incidence of dissociation reactions was reported to be about 23%.[21] Esketamine is available via the REMS program; patients must be monitored for 2 hours after nasal spray administration for safety.[22]

These findings regarding esketamine led to the development of psilocybin for TRD. The drug and product development process for psilocybin will likely take a similar approach. An initial open-label psilocybin study in patients with TRD (N = 12) was

conducted using 2 psilocybin doses of 10 mg and 25 mg.[23] The psilocybin doses selected for TRD are comparable to those for other psychiatric disorders under evaluation (**Table 1**).[2,17,24,25]

For the psilocybin TRD study,[23] treatment-resistant was defined as Hamilton Depression Rating Scale (HAM-D) scores > 17 and a lack of improvement with 2 different classes of antidepressant medications for at least 6 weeks within the current episode. A single dose of psilocybin 10 mg, followed by 25 mg 7 days later was administered. Clinical assessments were obtained at baseline, at 7 days with administration of the second dose, and at 3 months after the second dose. The primary efficacy outcome was determined by the Quick Inventory of Depressive Symptomatology (QIDS), and the secondary outcomes were determined by the HAM-D and Beck Depression Inventory (BDI).

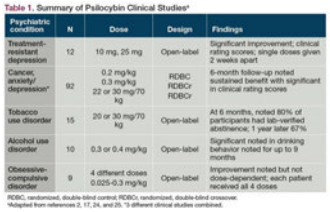

Table 1. Summary of Psilocybin Clinical Studies[a]

Psilocybin significantly reduced the mean (± SD) QIDS scores at 1 week (−11.8 ± 4.9, P = .002) and at 3 months (−9.2 ± 6.0, P = .003). The study also resulted in significantly reduced HAM-D and scores.[23] At the 1-week mark, remission (defined as reduction in BDI score of ≤ 9) was achieved in 8 patients (67%). At the 3-month follow-up, remission (defined as a 50% reduction in BDI scores) was achieved in 7 patients (58%); 5 patients (42%) reached complete remission. Psilocybin was well tolerated, with only mild transient confusion (N = 12) and/or transient anxiety (N = 9). Transient nausea (N = 4) was noted during the day of drug administration and subsided 1 to 2 days thereafter.

Because of these findings and the FDA's designation of psilocybin as a breakthrough therapy, a phase 2b clinical trial is underway in the United States and Europe (N = 216), with additional phase 3 clinical trials planned.[25] The phase 2b study design uses psilocybin 1 mg (considered placebo), 10 mg, and 25 mg, and the Montgomery-Asberg Depression Ratings Scales (MADRS) scores are considered the primary outcome.[17]

As the psilocybin pharmacologic mechanism of action involves 5-HT_{2A} receptor agonist effects, the study design for patients with TRD may differ from that of the esketamine program, in which antidepressants were continued. For the psilocybin clinical trials, the use of antidepressants or other medications may need to be discontinued for safety reasons and to prevent the possible development of serotonin syndrome.[26]

Another reason for antidepressant discontinuation is the suggestion that selective serotonin reuptake inhibitors (SSRIs) obstruct potential psilocybin benefits, as the pharmacological actions of an antidepressant may downregulate 5-HT_{2A} receptors.[2] The clinical psilocybin study may need to include a 2-week (at least) antidepressant withdrawal and washout phase to place patients, caregivers, and providers in a state of heightened alert to monitor and detect any significant changes in the patient's status. After psilocybin administration, the next question would be when to restart the antidepressant or other medications that were previously discontinued, with appropriate safety monitoring.

Other Potential Uses in Psychiatry

A summary of the other psychiatric disorders for which psilocybin has been assessed is shown in **Table 1**.[2,17,24,25] These studies enrolled only a small number of patients. Patients with cancer often have comorbid depression and anxiety and are associated with a poorer prognosis.[17,25] Patients with a variety of cancers in 3 clinical studies have been reported together. These 3 studies had a control group that used either psilocybin low-dose (1 or 3 mg) or niacin (250 mg), with a double-blind crossover or double-blind fixed-dose study design. In the 3 studies (shown in **Table 1**), each patient acted as their own control and had 2 treatment sessions in random order (either psilocybin 0.2 mg/kg first, and then niacin, or vice-versa) s[illegible]ced several weeks apart.

The second study was a crossover design that used psilocybin 22 mg/70 kg or 1 to 3 mg psilocybin/70 kg (instead of niacin). The third study used a crossover design with a higher single dose of psilocybin (0.3 mg/kg) and the placebo niacin in a randomized order, given 7 weeks apart. All 3 studies reported consistent results, in which psilocybin (not the low-dose group) produced significant decreases from baseline in depression (≥ 50% HAM-D scores) and anxiety (≥ 50% HAM-A scores) symptoms after 5 weeks, which persisted throughout the 6-month follow-up. Remission HAM-D and HAM-A scores were achieved by 65% and 57% of the participants, respectively. Studies of psilocybin use for depression, anxiety, and mood disorders associated with end of life are planned for phase 2 evaluation.[25]

Patients (N = 9) with treatment-resistant obsessive-compulsive disorder (OCD) were given 3 different psilocybin doses in a pilot study. The results showed significant decreases in the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for all doses without serious adverse effects.17 Testing for each dose was administered in a random order and conducted over 8 hours in a controlled environment, with a 1-week separation. The Y-BOCS and the visual analog scale (VAS) for overall OCD symptom severity were completed at baseline, 4, 8, and 24 hours post–drug administration. The Hallucination Rating Scale was given at the 8-hour time point, which showed a significant correlation with dose (P = .017) but lacked significant correlations with the Y-BOCS or VAS scores. Based upon these preliminary results, 2 ongoing randomized phase 2 clinical trials are underway to replicate these original findings.[25]

Both tobacco and alcohol use disorders have few therapeutic options; thus, pilot studies are exploring the use of psilocybin or such conditions (**Table 1**). Psilocybin has yielded significant improvements in abstinence, as measured by laboratory and behavioral assessments. In 1 pilot tobacco cessation clinical study conducted in 2017, participants entered a 15-week structured smoking cessation program and were given a single dose of psilocybin 20 mg at week 5, and 30 mg at week 7, with an optional 30 mg dose at week 13. Urinary cotinine levels (< 200 ng/mL) and exhaled carbon monoxide (≤ 6ppm) were used as the biomarkers for abstinence.

At the end of 6 months, 12 of the 15 (80%) participants remained abstinent; 10 (67%) participants remained abstinent at 1 year; and 9 (75%) at 2.5 years. This pilot study was expanded to enroll 95 individuals and is scheduled to be completed in 2021, depending upon enrollment.[25] The other pilot study assessed psilocybin's efficacy in alleviating alcohol dependence, which was defined as having at least 2 heavy drinking days in the previous 30 days. Participants received a total of 14 psychotherapy sessions. A single dose of psilocybin 0.3 mg/kg was given after the first 4 sessions, and a second single dose of 0.4 mg/kg was given after another 4 psychotherapy sessions. Each psilocybin administration session was completed under the Psychedelic-Assisted Psychotherapy procedure. (See the next section, Psychedelic-Assisted Psychotherapy Method and Microdosing.) Abstinence was based on self-reporting and was found to be significantly increased after the first psilocybin session. Moreover, abstinence was maintained for up to 9 months. The study was expanded to enroll up to 180 participants with completion scheduled for 2020 or 2021.[25]

Additional psilocybin clinical trials have been conducted for cocaine and opioid disorders, anorexia nervosa, and depression in early Alzheimer disease.[25] Another suggested therapeutic use of psilocybin may be for cluster headaches.[27]

Psychedelic-Assisted Psychotherapy

Unlike previous clinical trials in psychopharmacology, the use of psychedelic agents, such as psilocybin, LSD, and MDMA, will employ a therapeutic technique called "Psychedelic-Assisted Psychotherapy," which is summarized in **Table 2**.[25,28] This technique consists of 3 sections: preparatory, medication administration (1 to 3 sessions), and integration. In the preparatory section, the therapist or cotherapist team works with the patient to obtain a personal history, help the patient understand their symptoms, and prepare for the potential emotional or psychological impact of the agent.

During the medication session, a female-male cotherapy team is present to maintain integrity and safety, with the patient reclined in a chair or bed. For the next 6 to 8 hours, the therapists listen to the patient, while maintaining safety and facilitating trust and openness. Afterward, the therapists in the integration session work with the patient to interpret the psychedelic experience that arose, with the goal of making meaningful long-term changes. If the patient becomes highly agitated during the 6- to 8-hour period after psilocybin administration, while responding to the hallucinations or other psychological effects, a physician or nurse should immediately assess the need for either a single low-dose second-generation antipsychotic (eg, risperidone) or pimavanserin as a rescue medication.

Component	Process
Preparatory	Therapist or co-therapist team engages the patient and prepares them for the experience with an emphasis on potential emotional and psychological growth. Patient education of expectations during the psychedelic session is reviewed.
Medication	This process can have 1-3 sessions with moderate to high psilocybin doses. Therapists accompany the patient for safety and record the patient's comments and reactions. Drug is given in a comfortable room and patient is monitored for the next 6-8 hours. Therapist's goals are to maintain safety, trust, and openness.
Integration	Therapists work with patient to interpret the content of the psychedelic experience with meaningful long-term changes via identifying insights and interpreting thoughts or ideas that occurred during the session.

[a]Adapted from Reference 22.

Table 2. Summary of the Psychedelic-Assisted Psychotherapy Session[a]

Microdosing is another technique for psilocybin use. With this technique, about one-tenth of the full dose is used. Psilocybin dosing ranges are as follows: microdose, < 1 mg; very low dose, 3 mg; low dose, 8 mg; medium dose, 15 mg; and high dose, 22 mg or greater.[28] Although microdosing has been studied in small open-label studies with doses administered about once every 3 to 5 days, it is unclear how this technique differs from the full dose administered for depression and other psychiatric disorders.[29,30]

Concluding Thoughts

Psilocybin has received considerable renewed interest over the past few years and has been investigated as a treatment for TRD and other psychiatric conditions. Exploring the use of psilocybin for TRD and other potential therapeutic applications will be exciting, and would offer unique challenges for patients, mental health clinicians, as well as third-party reimbursement and regulatory agencies.

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Psychological and Cognitive Insight: How to Tell Them Apart and Assess for Each

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Jerrold Pollak, PhD
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The goal of this article is to provide an overview of psychological and cognitive insight, including working definitions for these and other insight-related constructs. The etiologies of compromised insight are outlined. This article also highlights clinically relevant correlates of psychological and cognitive insight.

Learning Objectives:

1. Clarify the similarities and differences between psychological insight and cognitive insight

2. Identify and define different types of pseudo-insight

3. Review common etiologies of compromised insight

4. Discuss the role of rating scales and psychological/neuropsychological testing in the evaluation of insight

TARGET AUDIENCE

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The evaluation of patients' insight into their own conditions has been a cornerstone of psychiatric practice for more than a century.[1] Most clinical studies and empirical investigations of insight have focused on patients' so-called psychological insight (sometimes referred to as *clinical insight*) and its role in the assessment and treatment of schizophrenia and other psychotic disorders. Since the early 2000s, the construct of *cognitive insight* has emerged as a complementary form and, like psychological insight, is considered to have important implications for research and clinical practice.[2]

Historically, assessment of patients' psychological insight has played a prominent part in differential diagnosis, case formulation, treatment planning, and decision-making. It has been considered an integral component of the mental status examination, intake evaluations, progress/treatment notes, and case closing summaries.

Since the advent of the stress tolerance and coping skills era of psychotherapy in the early 1990s, the construct of insight has played a less significant role in diagnosis and treatment planning. Still, the construct of insight remains an important factor to consider when utilizing a stress tolerance and coping skills approach to assessment and psychotherapy.

Psychological and Cognitive Insight

The reality is that there is no consensus definition for psychological insight. Broad and vague definitions are vulnerable to subjective judgment, low inter-rater reliability, and a high number of false positives, resulting in the overdiagnosis of insight-related problems. Narrower definitions risk generating unacceptably high rates of false negatives. This can lead to underdiagnosis of both the level and the severity of impaired insight and the erroneous conclusion that a patient has enough insight to benefit from a range of treatment options.

From a historical perspective, 3 components stand out: awareness that one has a mental disorder, the ability to correctly attribute one's symptoms to this condition, and the capacity to appreciate the need for treatment.[2] Additional components include an appreciation of the social and related consequences of one's illness.[3] For the purpose of this discussion, psychological insight can be gauged by the criteria in **Table 1**.[4]

Table 1. Criteria for Psychological Insight[4]

1. Some recognition of symptoms and related changes in mental status and everyday functioning
2. At least partial awareness of maladaptive perceptions, thoughts, beliefs, mood, or behavior, as well as unrealistic and skewed interpretations of remote, recent, and/or ongoing events and situations
3. A reasonable degree of concern about these difficulties and symptoms
4. Can attribute at least some difficulties and symptoms to one or more mental health conditions or other plausible health and medical-related factors
5. Appreciates the need for evaluation and treatment for difficulties and symptoms
6. Adequately understands the possible risks and benefits of the recommended treatment, including the consequences of declining treatment
7. Some ability to gauge the benefits and possible detrimental effects of ongoing treatment and capacity to work collaboratively with clinical staff
8. Can provide plausible explanations for wanting modifications to proposed treatment plan or for opting out of treatment altogether[4]

Table 1. Criteria for Psychological Insight[1]

Cognitive insight, unlike psychological insight, is a relatively recent arrival in the literature and has its genesis in the work of Aaron Beck, MD, and colleagues.[5] Cognitive insight comprises 2 components: self-reflection and self-certainty. The former refers to considering competing perspectives and entertaining alternative explanations for one's beliefs, ideas, and perceptions. The latter is the ability to be self-critical with respect to the correctness of one's beliefs, ideas, perceptions, and reasoning process. Self-certainty also includes a willingness to modify one's conclusions about self and others in response to support and empathetic feedback. Criteria for cognitive insight are included in **Table 2**.[6]

A Widespread Issue

Table 2. Criteria for Cognitive Insight[6]

1. Ability to remain objective about delusional ideas, other non-reality-based beliefs and experiences, and related cognitive misattributions and distortions
2. Capacity to put these difficulties and symptoms into perspective
3. Ability to be open and responsive to modifying one's perceptions, beliefs, and ideas
4. Capacity to be self-critical about one's beliefs and ideas

Table 2. Criteria for Cognitive Insight[6]

Decreased insight is fairly common among patients with a broad range of mental health, neurodevelopmental, and neurocognitive disorders. Decrements in psychological and cognitive insight are associated with a number of difficulties for patients, their loved ones, and the practitioners involved in their care. Insight-related difficulties also have significant implications for diagnosis, case formulation, and treatment. In addition, clinicians need to carefully assess the adequacy of a patient's level of psychological and cognitive insight in order to facilitate decision-making regarding informed consent to treatment, civil commitment, mandated outpatient treatment, child custody, parental fitness, work capacity, criminal responsibility, legal guardianship, estate planning, and assisted suicide.

What is generally referred to as *impaired insight* is prevalent among patients with schizophrenia, major mood disorders, and psychotic disorders. Although estimates vary, it seems at least 30% of these patients have compromised insight, which adversely affects their judgment and decision-making, response to treatment, functioning, and quality of life, as well as the attitudes and feelings of significant others.[7]

Insight might impact treatment choices, including level of care, alliance building, choice of treatment modalities, treatment adherence, and the overall course and outcome. For example, if a patient has a history of nonadherence due to persistently impaired insight associated with a psychotic disorder, a long-acting injectable antipsychotic medication may be used to enhance adherence.[8] Patients with impaired insight are also more responsive to supportive psychotherapy with distress tolerance and coping skills components than to insight-based psychodynamically oriented psychotherapy.

As well, both psychological and cognitive insight figure prominently in psychoeducation for caregivers and nonpsychiatric health care providers regarding the psychosocial and medical needs of patients with diminished insight.[9]

The Relationship Between Insights

Measures of psychological and cognitive insight correlate to a modest degree, suggesting that these 2 conceptualizations are relatively distinct (albeit overlapping) and complementary constructs.[2]

Cognitive insight differs from psychological insight because of its emphasis on meta-cognitive capacities and, more specifically, the patient's capacity for cognitive flexibility. These considerations encompass patients' awareness of the possible fallibility of their perceptions, beliefs, ideas, and thinking processes. It also includes the ability to hear corrective feedback and then use it to correct the maladaptive reasoning that underlies faulty conclusions about oneself and others.

Moreover, because cognitive insight includes the ability to entertain alternative explanations or viewpoints, it may ultimately undergird psychological insight. As patients' cognitive insight increases, they should be more aware of their illnesses and recognize salient symptoms and their real-world impact. In this regard, both of these types of insight may work in tandem to enhance self-understanding and treatment responsiveness.

Both psychological and cognitive insights are best understood as complex and interdependent multidimensional phenomena on a continuum and, hence, should be viewed as nonbinary.[10] Therefore, the question is not whether a patient possesses or lacks psychological or cognitive insight, but rather to what degree, if at all, they demonstrate self-awareness. In this regard, patients can have adequate or better insight into one or more aspects of their condition but not others.

For example, there is evidence that patients with schizophrenia appear to have better awareness of some of their psychiatric symptoms than of their associated cognitive difficulties.[7] Or, a patient may have a very limited understanding of the significance of their psychotic symptoms and decline intervention, but may be painfully aware of their depression and receptive to treatment for mood problems.

Thus, clinicians should use their estimation of a patient's psychological and cognitive insights to create both a case-specific profile of strengths and weaknesses germane to psychological self-reflection and an estimation of the patient's ability to work in a reasonably productive manner in treatment.[1]

Psychological and cognitive insight are dynamic rather than static constructs. A patient's insight profile may change over time in response to medical, psychological, and situational influences. A patient's insight may also fluctuate due to the frequency, duration, type, and severity of neuropsychiatric symptoms.

For instance, a young adult with acute onset of a suspected substance-induced psychotic disorder may display a pattern of uniformly impaired insight, but within a few days of supportive and targeted psychiatric treatment, the same patient may demonstrate substantial improvement on one or more insight components or parameters. Conversely, if a patient has waxing and waning insight-related difficulties due to a major mood disorder with intermittent psychosis and then suffers mild head injuries, they may exhibit a more widespread, persistent, and severe profile of impaired insight, referable to postconcussive factors. Therefore, it is important to periodically reevaluate the adequacy of insight.

Additional Conceptualizations

ANOSOGNOSIA. Psychological and cognitive insight overlap with the construct of anosognosia, which is defined as unawareness or denial of illness.[11] This term is generally limited to the detrimental effects of medical conditions that impair central nervous system functioning and adversely affect a patient's ability to recognize symptoms and their neurologic causes. It also has negative effects on daily functioning and quality of life. Problems with psychological and cognitive insight are considered an integral part of a patient's neuropsychiatric status. Additionally, anosognosia might be extended to describe the insight-related difficulties of patients with neuropsychiatric disorders such as schizophrenia (**Table 3**).[3]

PSEUDO-INSIGHT. This refers to patient reports suggesting greater recognition and understanding of their clinical status than is warranted based on history, collateral information, everyday functioning, recent/current life circumstances, and clinical judgment.

Table 3. Five Forms of Insight

■ Anosognosia	■ Usable insight
■ Pseudo-insight	■ Feigned illness
■ Alexithymia	

Table 3. Five Forms of Insight

In some instances, pseudo-insight represents a form of positive impression management. Patients may display pseudo-insight when seeking greater autonomy from real or perceived control by family or caregivers. Successful impression management can sometimes lead to quicker discharge from inpatient-level care, reduced involvement or termination of outpatient services and mental health court, and the voiding of conditional discharges from state hospitals.

In extreme cases, pseudo-insight can be associated with iatrogenic effects. This can occur when caretakers attempt to achieve quicker and more substantial gains in self-understanding than can be realistically assimilated and productively utilized, leading to a potentially serious worsening of the patient's clinical status.

Patients with psychotic disorders and personality disorders associated with a susceptibility to narcissistic injury (and accompanying precipitous loss of self-esteem, rage, dissociation, or transient psychosis) are especially vulnerable to destabilization in response to premature or overzealous efforts of clinicians to bolster insight. In particular, patients with borderline personality disorder are highly prone to negative therapeutic reactions, although this can also be observed in patients with other problematic personality patterns.[12]

Pseudo-insight can also be a problem after an initial psychotic episode, when patients may experience postpsychotic depression (anxiety, depression, lowered self-esteem, increased hopelessness, suicidal preoccupation, and reduced subjective quality of life). A mix of true and pseudo-insight often accompanies and influences this phase. It has also been tied to the pernicious influence of stigma as a mediating variable, including what is referred to as self-stigma or internalized stigma.[10] Postpsychotic depression is often accompanied by a mix of accurate insight into one's condition and pseudo-insight. The pernicious influence of stigma may be a mediating variable here, notably what is referred to as "internalized stigma."

There is also a variant of pseudo-insight that may be more aptly termed "deceptive insight," which involves persuasive and seemingly illuminating self-disclosures, frequently coupled with observations of others, that aim to manipulate and exploit others. Patients with salient antisocial or psychopathic traits frequently exhibit this form of pseudo-insight.

ALEXITHYMIA. Alexithymia, which roughly translates to "no words for feelings," involves a striking inability to make sense of and report one's feelings.[13] It is characterized by severe lifelong difficulty recognizing, labeling, describing, and expressing affective states, including psychological symptoms and other mental status change. These individuals have a characterological form of impaired insight, which may be aggravated by psychosocial or other stressors. It may worsen in response to the onset of neuropsychiatric disorder(s) of varied type.

USABLE INSIGHT. This concept refers to insight that flows from an ongoing treatment that is perceived as supportive and nonthreatening. It can be productively used by the patient to achieve desirable, real- world goals while maintaining hope for continued symptomatic and functional improvement. This insight has received increased attention in the literature on recovery trajectories in psychotic disorders. It potentially has broad application to many other psychiatric conditions, including substance use disorders, because improved insight appears to contribute to better treatment outcomes.[14]

FEIGNED ILLNESS. Feigned illness involves an exaggerated and, in some instances, fabricated account of poor daily functioning secondary to psychiatric or medical disorders. It can include reports of difficulties or symptoms that are compatible with impaired insight.[15] This clinical presentation appears to reflect "negative impression management." These patients may receive a diagnosis of malingering, when the motivation involves one or more external incentives, or of a factitious disorder, when the sick role is a salient motivating factor.

An Etiology of Insight

Impaired insight may result from major mental illnesses such as schizophrenia and other psychiatric conditions, notably major mood disorders with psychotic features that are associated with diminished awareness of illness. In many cases, limitations in insight are associated with long-standing neurodevelopmentally based cognitive and neuropsychological deficits, the onset of neurocognitive deficits during the prodromal psychotic phase, or a first episode of psychosis.[16]

In the case of anosognosia, reduced insight can result from an acute or insidious medically induced mental status change, referable to central nervous system dysfunction. This includes an acute mental status change referable to a right hemisphere cerebral vascular accident, which has well-documented negative effects on insight, and the deleterious effects of progressive neurodegenerative diseases such as Alzheimer disease and the behavioral variant of frontotemporal neurocognitive disorder.[17-19]

Impaired insight may also result from psychosocial or other stressors, which can heighten the effect of long-standing psychological defenses and associated coping strategies. That said, this explanation for diminished awareness of illness in schizophrenia and related disorders lacks clear empirical support and is not considered a sufficient explanation.[7]

Two or more etiologies can have a synergistic effect. For instance, an older adult with significant personality disorder, primarily involving one or more insight-interfering defenses (eg, denial, omnipotence, externalization of blame, projection, and/or projective identification), might develop a neurodegenerative disorder, which is also associated with diminished insight. In these circumstances, it is easy to misattribute the limitations in insight to the neurologic disorder. In fact, the patient's long-standing problematic defensive structure and coping mechanisms may be a contributory factor or even a sufficient explanation for the insight-related difficulties. This is not rare, especially early in the neurodegenerative disease process.

Along similar lines, limitations in insight frequently co-occur as part of the long-term baseline functioning of patients with neurodevelopmental disorders such as intellectual disability and autism spectrum disorder, even when these conditions are mild. Kindred conditions, like borderline intellectual functioning, are also highly associated with baseline decrements in insight. In some instances, this can lead to an overdiagnosis of an acquired impairment in insight.

A reliable history (via record review or collateral interviews with significant others) that includes neurodevelopmental status, personality patterns and traits, and general adaptation to life preceding illness onset is needed to determine the root cause of a patient's impaired insight. Reports of previous psychological and neuropsychological test evaluations can also be helpful.

Correlates of Insight

Clinical literature and empirically based studies find many unfavorable consequences of impaired insight.[2] Most of this literature pertains to psychological insight involving patients with psychotic disorders, in particular schizophrenia. Impaired insight has many negative consequences for patients' mental health, careers, and social lives (**Table 4**).[3,14,20,21]

These negative consequences make intuitive sense and continue to influence clinical practice. However, there is only modest empirical support for many of them. Moreover, most of the research study data are correlational and, hence, insufficient to clearly establish cause and effect relationships. For example, is poor treatment adherence caused by decrements in insight or do difficulties with treatment adherence result in problems with insight?[14]

Table 4. Ramifications of Reduced Insight[3,14,20,21]

1. Decreased help-seeking behavior
2. Increased frequency and duration of untreated illness
3. Difficulty establishing workable treatment alliances
4. Poor adherence to treatment
5. More frequent and severe symptoms
6. Recurrent episodes of acute illness
7. Increased use of emergency mental health services and psychiatric admissions (notably civil commitments)
8. Worse treatment and a poorer prognosis
9. Lower educational and vocational attainment
10. Difficulty establishing and sustaining meaningful interpersonal relationships
11. Poorer everyday function and quality of life

Table 4. Ramifications of Reduced Insight[3,14,20,21]

Regarding schizophrenia and psychological insight, there are positive correlations between higher levels of insight and greater adherence to treatment.[14] Higher insight also correlates with improved indices of general mental health and better daily functioning over time. On the other hand, there are negative correlations between lower levels of insight and increased frequency of positive and negative psychotic symptoms, greater disorganized thinking, and increased rates of psychiatric hospitalization.

Additional empirical research on psychological insight is indicative of mixed findings regarding insight and indices of quality of life and functioning. Results have included both positive or negative correlations and no linkages between insight and these variables.[22]

Empirical research on cognitive insight has found negative correlations between the self-reflectiveness component of cognitive insight (an indicator of higher cognitive insight) and positive symptoms of psychosis.[2] Notably, these symptoms are more frequent among patients with lower self-reflectiveness. Findings are also consistent with the expected linkage between the self-certainty component of cognitive insight (an indicator of lower cognitive insight) and positive symptoms of psychosis, which

are more frequent among patients with higher self-certainty. There are mixed findings regarding the relationship between cognitive insight and indices of quality of life and adequacy of daily functioning.

There is a continuously expanding body of research on the cognitive and neuropsychological correlates of insight. As is true with most other research endeavors pertaining to insight, the most widely studied form of insight is psychological insight. Most investigations have involved patients with schizophrenia and related psychotic disorders.[23]

With few exceptions, most studies of patients with schizophrenia report significant and persistent decrements in cognitive and neuropsychological functioning that encompasses general cognitive and intellectual abilities and skills, sustained attention and concentration, anterograde-episodic memory, and executive functioning.[24]

Still, patients' neurocognitive profiles show considerable heterogeneity, and small numbers of patients with schizophrenia have minimal or no discernible neurocognitive deficits based on detailed psychometric testing.[23]

Cognitive and neuropsychological functioning should be related to the adequacy of psychological insight. That is, better neurocognitive functioning should be correlated with higher levels of insight, and worse neurocognitive functioning should be linked with lower levels of insight. Overall, studies offer reasonable evidence for this prediction and support the idea that cognitive and neuropsychological deficits are meaningfully related to decrements in accurate self-appraisal.[22]

Still, the linkages are far from robust. This suggests that neurocognitive factors are probably not sufficient to explain the high base rates of impaired insight in schizophrenia and psychotic disorders. This underscores the importance of adopting a biopsychosocial perspective when it comes to understanding the relationship of insight to schizophrenia and other mental disorders, and when considering the development of effective strategies to augment insight.[23]

Negative correlations have been reported between levels of psychological insight (specifically cognitive difficulties related to having a psychotic disorder) and degrees of neurocognitive impairment.[25]

Finally, a review of the correlates of cognitive insight found fairly good support for an association between higher levels of self-certainty and worse neurocognitive functioning.[2] That review also highlights mixed findings when it comes to the expected positive correlation between the self-reflectiveness component of cognitive insight and neurocognitive functioning (namely, that higher levels of self-reflectiveness are associated with better neurocognition). More specifically, higher self-reflectiveness was associated with more compromised neurocognition.[2]

Insight and the DSM-5

An innovative feature of the DSM-5 is the introduction of specifiers, which are designed to provide a more fine-grained description of a patient's diagnostic status. A specifier for insight is based on the following classification: good or fair insight, poor insight, and absent insight or delusional beliefs. This specifier is indicated for 3 of the 9 disorders contained in the chapter titled "Obsessive-Compulsive and Related Disorders." It remains unclear why only 3 diagnoses and this category of disorders have these specifiers, because many DSM-5 categories include conditions that can present with varying degrees of problematic insight, including neurodevelopmental disorders, dissociative disorders, somatic symptoms and related disorders, feeding and eating disorders, personality disorders, substance-related and addictive disorders, and neurocognitive disorders.[26]

Assessment and Tracking Tools

There is no gold standard assessment protocol or tool(s) for evaluating insight, but there are a number of self-report and clinician rating scales that have been developed since the 1990s.[27] All have their strengths and weaknesses, and none are appropriate

for all patients.

Most rating scales have been developed for the assessment of psychotic and related disorders and are not clearly applicable to patients with suspected or known decrements in insight. Some scales measure a limited number of components of awareness, judgment, and thinking germane to insight. For example, the Measure of Insight into Cognition-Clinician rating scale is specifically designed to assess insight related to cognitive difficulties and symptoms in patients with schizophrenia.[25]

Similarly, many scales are not designed for longitudinal assessment over the course of treatment. Some are geared more to one form of insight than another. For example, the Beck Cognitive Insight Scale is designed for the assessment of cognitive insight, whereas most scales were developed for the evaluation of psychological insight.[5]

Scales for the assessment of psychological insight intercorrelate reasonably well, which suggests that they are measuring comparable aspects of this construct. However, correlations between self-report and clinician and observer scales are modest, indicating that there are important discrepancies between patient self-appraisal and clinician judgment regarding insight.[14]

Unfortunately, the majority of these instruments have, at best, a limited normative base. Many do not have operational criteria for classifications based on level of severity (eg, impaired/poor, fair, good), which would strengthen interscorer reliability. Moreover, few instruments generate empirically derived cut-off scores for classifications (normal versus abnormal, impaired versus intact) or involve score profiles offering clear guidelines for diagnosis and treatment planning and intervention.

Self-reported rating scales are not stand-alone instruments and should only be used to supplement findings from clinician-based rating scales, clinical and semi-structured interviews, and collateral data from record reviews and informants. Clinical judgment is needed to properly utilize these scales for diagnosis, treatment planning, and longitudinal assessment.

It may be necessary to perform formal psychological and neuropsychological testing. These tests include self-reporting instruments such as the Minnesota Multiphasic Personality Inventory-3 (MMPI-3), the Personality Assessment Inventory (PAI), and the Million Clinical Multiaxial Inventory-IV (MCMI-IV). They contain scales and indices relevant to the assessment of insight (including pseudo- and deceptive insight). Formal psychological and neuropsychological testing should be considered when the patient's clinical status remains unclear following appropriate assessment or when there is some question about personality and psychodynamic or cognitive and neuropsychological factors that contribute to the patient's insight-related difficulties/symptoms. Formal testing might also follow repeated unexplained stalemates in treatment or difficulties with treatment adherence that may reflect heretofore unappreciated problematic insight.

Directions for Future Research

The clinical and empirical study of insight has largely been confined to psychotic disorders utilizing the construct of psychological insight. Therefore, considerably less is known about insight (both psychological and cognitive) in relation to mood and other disorders like obsessive-compulsive disorder.[28] There are scant data bearing on the interface of insight with nonpsychotic disorders.

A key research agenda should include the development of empirically validated strategies to enhance cognitive and psychological insight across a range of disorders. Future research should help clinicians reliably differentiate state-related from trait-related decrements in insight. Promising interventions include psychoeducation (with both patients and caregivers), cognitive-behavioral approaches, motivational interviewing, and cognitive remediation.[7,24,29]

Future research should aim to better understand the therapeutics of insight, including whether specific interventions may be more effective in enhancing insight with certain patient groups. Further, it would be useful to understand which approaches may be more efficacious than others with certain components of impaired insight and during different phases of illness and stages of treatment.[3,30]

As for nonpsychotic disorders, it would be helpful to ascertain the base rates of compromised psychological and cognitive insight in these patients, and whether there are any clinically relevant differences in the level and pattern of insight-related difficulties between psychotic and nonpsychotic disorders and, more generally, across diagnostic categories.

To address these gaps in knowledge, it would be highly desirable to have clinician and patient rating scales that generate score profiles for both psychological and cognitive insight.

Rating scales that are germane to both forms of insight could help to determine whether measuring both at once would improve incremental validity. Multiple-form rating scales could contribute to more successful treatment planning and outcomes among one or more patient groups than rating scales that address only one type of insight.

Work groups tasked with the development of an updated *DSM* should consider inclusion of a clinical and research review of insight and its application to differential diagnosis.

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Investigator's Brochure

PRODUCT: Psilocybin, [3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate

IND#: 129532

VERSION: 3.0

RELEASE DATE: 31 August 2020

REPLACES: 2.0 (17 December 2018)

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Psilocybin Investigator's Brochure Amendments

DOCUMENT HISTORY	
Document	**Date**
Original Psilocybin Investigator's Brochure Version 1.0	07 February 2018
Version 2.0	17 December 2018
Version 3.0	31 August 2020

Summary of Changes, Version 2.0

- Section 5.3.1. Introduction: Articulation of number of subjects exposed to psilocybin compared to number of doses administered
- Section 5.3.5.2.1. QTc: University of Wisconsin Study additional analysis of the effect of psilocybin concentration on QTc interval prolongation
- Section 6.5.6. Abuse Potential: Updates around the abuse potential for psilocybin from published literature (Heal, Gosden, & Smith, 2018; Johnson, Griffiths, Hendricks, & Henningfield, 2018)

Summary of Changes, Version 3.0

- Formatting changes
- Tables renumbered
- Table 5.3-4: List of complaints 24 hours post-dose: Corrected unit values in first row (mg to µg)
- Section 4.3, Non-Clinical Toxicology: Added Usona genetic toxicology studies PSIL-GEN-101 and PSIL-GEN-102
- Section 5.3.4, Clinical Trials for Depression and Anxiety: Added Usona clinical studies PSIL201 and PSIL201-LTFU

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USONA INSTITUTE

Usona Institute is a non-profit medical research organization founded in 2014. Usona Institute conducts and supports biochemical and clinical research to further the understanding of the therapeutic effects of psilocybin and other consciousness-expanding medicines. Usona has developed psilocybin for oral administration (25 mg, single-dose) in conjunction with a supportive set and setting protocol for major depressive disorder (MDD). Additional information about Usona can be found at www.usonainstitute.org.

ABBREVIATIONS

AE	Adverse event
API	Active Pharmaceutical Ingredient
ASC	Altered State of Consciousness
AUC	Area Under the Curve
BDI	Beck Depression Inventory
BP	Blood Pressure
BPM	Beats Per Minute
BSI	Brief Symptom Inventory
C	Celsius
CI	Confidence Interval
CRU	Clinical Research Unit
CTCAE	Common Terminology Criteria for Adverse Events
d	Cohen's d effect size
DBP	Diastolic Blood Pressure
DEA	Drug Enforcement Agency
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5	Diagnostic and Statistical Manual of Mental Disorders - Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
ECT	electroconvulsive shock
EGR1	early growth response protein 1
FDA	Food and Drug Administration
fMRI	Functional magnetic resonance imaging
GAD	Generalized Anxiety Disorder
GAF	Global Assessment of Functioning
HADS	Hospital Anxiety and Depression Scale HAM-A Hamilton Anxiety Scale
HAMD	Hamilton Depression Rating Scale HED human equivalency doses
HPMC	hydroxypropyl methyl cellulose Hopkins Johns Hopkins University
HPPD	Hallucinogen Persisting Perception Disorder
hr	Hour
IND	Investigational New Drug
IB	Investigator's Brochure
LAP-R	Life Attitude Profile-Revised
LD_{50}/ED_{50}	The ratio of the lethal dose in 50% of the population to the effective dose in 50% of the population
LOT-R	Life Orientation Test-Revised LSD Lysergic Acid Diethylamide
MADRS	Montgomery-Asberg Depression Rating Scale

MDD	Major Depressive Disorder
MDMA	3,4-methylenedioxy-methamphetamine min Minute
mg	Milligram
mg/kg	Milligrams per Kilogram
mm Hg	Millimeters of Mercury
MMRM	Mixed Methods for Repeated Measures
MQOL	McGill Quality of Life
N	Sample Size
ng/mL	Nanograms per Milliliter
NSDUH	National Survey on Drug Use and Health
NYU	New York University
OCD	Obsessive Compulsive Disorder
p	*p*-value
PEA	Phenethylamine
PET	Positron Emission Tomography
POMS	Profile of Mood States
QIDS	Quick Inventory of Depressive Symptomatology
SAE	Serious Adverse Event
SAMHSA	Substance Abuse and Mental Health Services Administration
SBP	Systolic Blood Pressure
SCID	Structured Clinical Interview for DSM-IV Axis I Disorders
SEM	Standard Error of the Mean
SHAPS	Snaith-Hamilton Pleasure Scale
STAI	State-Trait Anxiety Inventory
SNRI	Serotonin-norepinephrine reuptake inhibitors SSRI Selective serotonin reuptake inhibitor
t	Student's t-test
TRD	Treatment-Resistant Depression
vs	Versus
UCLA	University of California at Los Angeles
µg/kg	Microgram per Kilogram
UGTs	UDP-glucuronosyltransferase
US	United States
USP	United States Pharmacopeia
UW	University of Wisconsin-Madison
VAS	visual analog scale
YBOCS	Yale-Brown Obsessive Compulsive Scale
ZPES	Zeeh Pharmaceutical Experiment Station

1. SUMMARY

This Investigator's Brochure (IB) describes the physical, chemical, and pharmacological characteristics of psilocybin, its effects in non-clinical and clinical studies, and the safety profile of psilocybin administered under supportive conditions within the clinical research setting. It summarizes relevant information for the investigator to consider regarding the use of psilocybin in an accompanying clinical protocol detailing study design and conduct. All relevant non-clinical and clinical data from published and unpublished research studies supporting psilocybin's safety and potential efficacy have been provided. This IB will be reviewed annually and amended as further information becomes available.

Psilocybin (3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate) is a natural product produced by numerous species of *Psilocybe* mushrooms, which is manufactured for clinical use to control potency and purity. It is a tryptamine derivative, and in humans the phosphate group is rapidly enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors, the most important of which in this setting is the 5-HT2A receptor (Carhart-Harris et al., 2014; Nichols, 2004). Oral psilocybin has about a 50% bioavailability and psilocin is detectable in plasma within 20 minutes of administration of the parent compound (Brown et al., 2017; Hasler, Bourquin, Brenneisen, Bär, & Vollenweider, 1997). The half-life of psilocin in blood is 2-3 hours. Onset of noticeable psychoactive effects occurs within one hour, peaks at about two hours after a dose, and loss occurs typically around six hours after the dose. Based on this time course, in the clinical trial setting, protocols mandate observation until approximately 8 hours after dosing.

Psilocybin reliably induces profound changes in sensory perception, emotion, thought, and sense of self, characterized by marked alterations in all mental functions, including perception, mood, volition, cognition and self-experience (Geyer & Vollenweider, 2008; Studerus, Kometer, Hasler, & Vollenweider, 2011). These profound changes are often referred to as mystical-type experiences. Measures of mystical-type experience occurring during psilocybin treatment have been repeatedly observed to predict later effects on behavior and emotions, including reductions in depressive and anxious symptoms (Griffiths et al., 2016; MacLean, Johnson, & Griffiths, 2011; Ross et al., 2016).

Non-clinical *in vivo* and *in vitro* studies, found via literature searches, demonstrate that similar to humans, when psilocybin is administered orally to rats it is rapidly dephosphorylated to psilocin in the intestinal mucosa by alkaline phosphatase and a nonspecific esterase, with approximately 50% of the total volume of psilocin absorbed from the digestive tract (Kalberer et al., 1962). Maximum plasma levels are achieved after approximately 90 minutes (Chen et al., 2011). When administered systemically (i.e., bypassing the gut), initial psilocybin metabolism is performed by tissue phosphatases, with in vitro studies indicating the kidneys as being among the most active metabolic organs (Horita & Weber, 1961). Across species tested, the highest levels of psilocin were found in the neocortex, hippocampus, and thalamus (Hopf & Eckert, 1974).

Recent clinical studies utilizing pharmaceutical-grade oral psilocybin under controlled conditions have been performed upon healthy participants and various subpopulations in order to gauge safety events and preliminary clinical efficacy. Though the safety reporting criteria and the level of data verification varied greatly between studies, including many participant-reported outcomes, these data have been utilized to elucidate the expected adverse event (AE) profile of psilocybin. The

clinical studies summarized in this IB present similar safety profiles, with both psychological and physical adverse events reported. The most common adverse psychological events included anxiety, negative emotional states and paranoid/delusional thinking during dosing sessions, and the most common physical effects were increased blood pressure (BP) and heart rate, mild nausea, and mild headache.

Preliminary efficacy of psilocybin in these studies showed a decrease in symptomatic response in indications including obsessive compulsive disorder (OCD), substance use disorder, depression, and anxiety. Overall, psilocybin has been well-tolerated at the doses examined in the clinic. Due to the psychoactive nature of the compound, it should only be administered in a controlled setting and per the accompanying clinical protocol.

Please note that this IB was written to support Usona-sponsored studies under IND 129532 as governed by U.S. law and regulations. Other investigators referencing this document may need to adjust certain details as appropriate to their own studies or local regulations.

2. INTRODUCTION

2.1. Interventional Approach

2.2. Psilocybin Background

Psilocybin 3-[2-(dimethylamino) ethyl]-1H-indol-4-yl] dihydrogen phosphate is a natural product produced by numerous species of *Psilocybe* mushrooms. The phosphate group is enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors, the most important of which, for its behavioral effects, is the 5-HT2A receptor (Carhart-Harris et al., 2014; Nichols, 2004). Psilocybin was first isolated from *Psilocybe* mushrooms in 1957, followed by *de novo* synthesis in 1958 (Passie, Seifert, Schneider, & Emrich, 2002). It was marketed worldwide in the 1960s as *Indocybin*™ for experimental and psychotherapeutic purposes. Although it was well tolerated and demonstrated potentially useful effects, it was classified as a controlled substance in the U.S., placed in Schedule I in 1970, and effectively removed from clinical use or scientific study. Psilocybin, and similar drugs such as lysergic acid diethylamide (LSD) and mescaline, fall into a pharmacological class that we refer to in this application as "classic psychedelics" to differentiate them from other psychoactive substances (ex. 3,4-methylenedioxy-methamphetamine; MDMA) that have different psychological/behavioral effects and different adverse effect profiles and risk/benefit ratios than psilocybin (Carhart-Harris & Nutt, 2013; Nutt, King, Phillips, & Independent Scientific Committee on, 2010).

Several lines of evidence suggested that serotonergic hallucinogens, such as psilocybin, have clinical potential for inducing therapeutically-beneficial behavior change in a variety of psychiatric conditions. Results of completed and published studies are reported.

2.3. Importance of a Supportive Set and Setting Protocol

Due to the psychoactive nature of psilocybin, the safety of participants in clinical trials can be enhanced by testing psilocybin within a "set and setting" protocol (Lyons & Carhart-Harris, 2018). By addressing the *set* (the emotional/cognitive/behavioral state/mindset and expectations of study participants just prior to psilocybin exposure) and *setting* (the physical environment in which the exposure occurs) of the experience, the risk of the subject reporting an event which was distressing or injuring themselves can be reduced. This approach generally incorporates three components: 1) preparation, 2) drug session, and 3) post session meetings to integrate the classic hallucinogen experience.

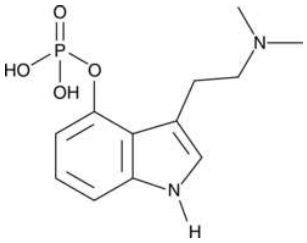
In the first phase, participants undergo pre-exposure preparation sessions designed to build rapport with the facilitators who would be present during the drug exposure session and to identify personal themes and struggles that might be especially likely to impact the session experience. In the second phase, the drug session itself is conducted by two facilitators (typically a male and female) who are present throughout the session. Sessions are typically conducted in a room designed to be quiet, comfortable, and aesthetically pleasing, and participants are encouraged to wear eyeshades and listen to a program of music through headphones during the drug exposure to aid them in focusing their attention inward. In the third phase, participants are engaged in a series of drug-free interview meetings of variable frequency, sometimes over a period of several weeks, to discuss their session experience thoroughly with the goal of maximizing its therapeutic benefit.

3. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1. Chemical Name and Structure of Investigational Substance

[3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate

Figure 3.1-1: Molecular structure of psilocybin.



3.2. Description of Investigational Substance

Psilocybin is a tryptamine derivative presenting as a white crystalline solid with a melting point of 220-228°C. It is stable over extended periods in dark storage at controlled room temperature. Psilocybin is soluble in 20 parts boiling water or 120 parts boiling methanol.

3.3. Description of Investigational Product

For use in Usona sponsored clinical studies, psilocybin is provided as 25 mg capsules (size 2, hydroxypropyl methyl cellulose (HPMC), white).

3.4. Description of the Placebo

For use in Usona sponsored clinical studies, the placebo niacin, also known as vitamin B3, is provided as 100 mg capsules (size 2, HPMC, white). Niacin is United States Pharmacopeia (USP)-grade and sourced from a commercial nutritional supplement vendor.

3.5. Storage and Handling

Both placebo and psilocybin capsules are packaged individually into high-density polyethylene bottles (30 cc) and labelled in a double-blind fashion with appropriate randomized codes. Bottles must be maintained at room temperature in a locked, secure location within the research pharmacy at the site and in accordance with Drug Enforcement Agency (DEA) regulations. Study staff with access to the psilocybin inventory will be pre-defined.

3.6. Administration of Investigational Product

Capsules should be administered orally, with water, per the associated clinical protocol. Capsules should not be opened or chewed.

4. NON-CLINICAL STUDIES

Non-clinical studies summarized in this section were pooled from literature searches and include *in vitro* analyses, as well as *in vivo* studies involving rats, mice, cats and rhesus macaques. Psilocybin doses utilized in the studies varied, and do include some within range of a 25-mg oral dose (0.36 mg/kg in a 70-kg individual) for clinical use, based on standard animal-to-human dose equivalency.

4.1. Non-Clinical Pharmacology

When administered acutely, psilocybin has been shown to induce new behaviors in animals. These behaviors were subsequently tested following attenuation or inactivation of associated serotonin receptors to test for interaction with psilocin. Head twitching behavior, exhibited by rodents and similar to psychedelic effects in humans, was found to be blocked by pharmacologic inactivation of the 5HT2A receptor (Willins & Meltzer, 1997). Most, but not all, of the other behaviors induced by psilocybin in animals (Table 4.1-1) are similarly blocked or significantly attenuated by inactivation of the 5HT2A receptor, either pharmacologically or via gene knock-out. However, *in vitro* psilocybin binds to a wide range of receptors in addition to 5HT2A, including (ordered by increasing binding affinity): 5HT2B, 5HT1D, dopamine D1, 5HT1E, 5HT1A, 5HT5A, 5HT7, 5HT6, D3, 5HT2C, and 5HT1B (Ray, 2010). In rodents, behaviors not impacted by 5HT2A inactivation include locomotor inhibition, which appears to be mediated by 5HT1A and 5HT2B/C receptors, based on antagonist studies.

Table 4.1-1: Behaviors exhibited by animal species upon psilocybin administration

Animal Species	Behaviors Exhibited
Rodent	Head-twitching, discrimination of psilocybin from non-psychedelic psychoactive compounds, inhibition of locomotion, disruption of short interstimulus interval (ISI), prepulse inhibition of startle (PPI), enhancement of long ISI PPI, reductions in aggression/dominance, enhancement/impairment of memory consolidation and retrieval (task dependent)
Cat	Head shaking, staring, clonic muscle activity, investigatory or play behavior
Monkey	Increased transient self-administration of psilocybin

In the rat brain, electroencephalographic changes induced by psilocybin were partly normalized by antagonists of 5-HT1A, 5HT2A/C as well as dopamine D2 receptors (Tylš et al., 2014). Agonism at 5HT1A autoreceptors also appeared to account for psilocybin-induced inhibition of dorsal raphe nucleus activity (Aghajanian & Hailgler, 1975), although no association was observed between dorsal raphe inhibition and any measure of behavior in freely-moving cats (Trulson et al., 1981). Autoradiographic evidence shows that after systemic administration in the rat, psilocin concentrates in the neocortex, the hippocampus, and the thalamus, while showing much lower values in the hypothalamus and striatal regions (Hopf & Eckert, 1969). A single study found that doses of psilocybin within range of a 25 mg oral dose in humans (based on standard animal-to-human dose delivery) reduced neurogenesis in the rat dentate gyrus of the hippocampus, as did the 5HT2A antagonist ketanserin (Catlow et al., 2013). An *in vitro* study of rat hippocampus reported that application of psilocybin reduced neuronal spike activity in hippocampal CA1 pyramidal neurons, consistent with a suppression of glutamate transmission in that brain structure (Moldavan et al., 2001).

In addition to effects on serotonin neurotransmission, non-clinical studies suggest that psilocybin also has effects on other brain systems/chemicals that may be of behavioral relevance. In awake rats a microdialysis study found that systemically administered psilocin significantly increased extracellular dopamine, but not serotonin, levels in the nucleus accumbens (Sakashita et al., 2015). Conversely, systemic administration of psilocin significantly increased extracellular serotonin levels in the rat medial prefrontal cortex, but dopamine was decreased in this region. Neither extracellular dopamine nor serotonin levels in the ventral tegmental area were altered by administration of psilocin. Psilocybin has also been reported to reduce norepinephrine levels in the rat hypothalamus, although this effect was not associated with behavioral alterations induced by the drug (Sugrue, 1969). Psilocybin increased plasma prolactin levels in a serotonergically-dependent fashion (Meltzer et al., 1978).

4.2. Non-Clinical Pharmacokinetics

Similar to human pharmacokinetics (Section 5.1) studies in rats demonstrate that upon ingestion psilocybin is rapidly dephosphorylated to psilocin in the intestinal mucosa by alkaline phosphatase and a nonspecific esterase, with approximately 50% of the total volume of psilocin absorbed from the digestive tract (Kalberer et al., 1962). When administered systemically (i.e. bypassing the gut), initial psilocybin metabolism is performed by tissue phosphatases, with in vitro studies indicating the kidneys as being among the most active metabolic organs (Horita & Weber, 1961). Psilocin metabolism occurs primarily via endoplasmic enzymes UDP-glucuronosyltransferase (UGTs), which produce psilocin-O-glucuronide (Manevski et al., 2010). Of 19 recombinant UGTs thathave been evaluated, UGT1A10 in the small intestine and UGT1A9 in the liver have been shown to have the greatest activity (Manevski et al., 2010).

Following oral administration of psilocybin in rats, maximum plasma levels are achieved after approximately 90 minutes (Chen et al., 2011). Psilocin is distributed to all tissues, including the brain (maximum concentration at one hour post dose), and is excreted within 24 hours, with the majority excreted within the first eight hours (65% in the urine, and 15–20% in the bile and feces) (Kalberer et al., 1962; Hofmann, 1968). Across species, the highest levels of psilocin were found in the neocortex, hippocampus and thalamus (Hopf & Eckert, 1974). In mice, psilocin accumulates in the kidneys and the liver prior to appearing in the brain (Hopf & Eckert, 1974; Horita & Weber, 1962).

4.3. Non-Clinical Toxicology

Non-clinical studies to date suggest that psilocybin has very low toxicity, consistent with its repeated safe administration in clinical studies in humans (Nichols et al., 2016). Early studies examining isolated organs (e.g. intestine, heart) from guinea pigs and rats exposed to high doses of psilocybin (i.e. > 25 mg for humans, using standard animal-to-human dose equivalency) (Cerletti, 1958). Non-clinical studies of the neurotoxicity of psilocybin have not been conducted, per literature review. A study of rats found the LD50 for psilocybin to be between 280-285 mg/kg, which is far higher than a 25-mg dose in humans (0.36 mg/kg in a 70-kg individual). Based on standard human equivalency doses (HED), the LD50 in rodents is approximately 5,000 times the dose that a 70-kg human would receive in the current IND. The LD50 of psilocin, the active first metabolite of psilocybin, is significantly lower for rodents than the LD50 of psilocybin itself, being 75 mg/kg. The ratio between the LD50 and ED50 is 641 per the National Institute for Occupational Safety and

Health Registry of Toxic Effects (Tylš et al., 2014), which compares favorably with many drugs approved for human use (e.g. aspirin has an LD50/ED50 of 199). When administered to awake animals (including rats, mice, rabbits, cats and dogs) at a dose of 10 mg/kg (significantly higher in all species than a 25 mg dose in humans) autonomic effects were induced that included mydriasis, piloerection, irregularities in heart and breathing rate and hyperglycemia (Cerletti, 1958; Steiner & Sulman, 1963) that were time limited and completely resolved following exposure. Similar autonomic effects were observed when psilocybin at a dose of 1-4 mg/kg (all doses higher than dose for this Investigational New Drug (IND)) was administered to baboons (Meldrum & Naquet, 1971).

Although the mutagenicity risk of psilocybin has not been definitively established, a study that utilized the micronucleus test in mice and administered psilocybin dosages of 4-16 mg/kg (significantly higher than a 25 mg dose in humans) found no evidence of genetic abnormalities, based on an absence of chromosome breakage (Van Went, 1977).

As of August 2020, two GLP-compliant genotoxicity studies with psilocybin have been conducted by Usona Institute: a bacterial reverse mutation assay (PSIL-GEN-101) and an *in vitro* micronucleus assay (PSIL-GEN-102). These two studies are summarized in Table 4.3-1 and further described below.

Table 4.3-1: Completed genotoxicity studies with psilocybin

Study Description	Test Formulation	Test Organisms/ Species	Dose/ Concentration (µg/mL)	Result	GLP
Bacterial Reverse Mutation Test	Psilocybin in purified water	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and TA102	0, 5, 16, 50, 160, 500, 1600, 5000	Negative	Yes
In Vitro Micronucleus	Psilocybin in purified water	Human peripheral blood lymphocytes	200, 240, 284.1	Negative	Yes

GLP: Good Laboratory Practice

Bacterial reverse mutation test (PSIL-GEN-101): Seven concentrations of psilocybin were assayed for mutation in five histidine-requiring strains (TA98, TA100, TA1535, TA1537 and TA102) of *Salmonella typhimurium*, both in the absence and in the presence of metabolic activation by an Aroclor 1254-induced rat liver post-mitochondrial fraction (S-9). No evidence of mutagenic activity was seen at any concentration of the drug substance with or without the S9 metabolizing system. Psilocybin was not mutagenic in the bacterial reverse mutation tests at concentrations up to 5,000 µg/plate.

***In Vitro* Micronucleus test in Human Lymphocytes (PSIL-GEN-102):** This study tested psilocybin drug substance at concentrations of 200, 240 and 284.1 µg/mL in cultures of human peripheral blood lymphocytes from pooled blood of two male donors. The highest concentration tested, 284.1 µg/mL (equivalent to 1 mM), was determined from a preliminary cytotoxicity range-finding experiment.

Treatment of cells with psilocybin for 3+21 hours in the absence and presence of S-9 and for 24+24 hours in the absence of S-9 resulted in frequencies of micronucleated binucleate (MNBN) cells that were similar to and not significantly higher (at the $p \leq 0.05$ level), compared to those observed in the concurrent vehicle controls, at all test article concentrations analyzed under each treatment condition and there were no statistically significant linear trends (Table 4.3-2). It was concluded that psilocybin did not induce micronuclei in cultured human peripheral blood lymphocytes when tested up to a concentration equivalent to 1 mM in this *in vitro* cytogenetic test system.

Table 4.3-2: Frequency of Micronucleated Binucleate Cells in *In Vitro* Micronucleus Assay with Psilocybin

Treatment	Concentration (µg/mL)	Cytotoxicity (%) [1]	Mean MN Cell Frequency (%)	Historical Control Range (%) [2]	Statistical Significance
3+21 –S-9	Vehicle [3]	-	0.45	0.00 to 0.70	-
	200.0	0	0.60		NS
	240.0	0	0.50		NS
	284.1	0	0.40		NS
	MMC, 0.30 [4]	38	7.15		$p \leq 0.001$
3+21 +S-9	Vehicle [3]	-	0.40	0.10 to 0.90	-
	200.0	0	0.50		NS
	240.0	0	0.25		NS
	284.1	0	0.40		NS
	CPA, 5.00 [4]	52	3.20		$p \leq 0.001$
24+24 –S-9	Vehicle [3]	-	0.25	0.00 to 0.80	-
	200.0	3	0.50		NS
	240.0	7	0.35		NS
	284.1	6	0.30		NS
	VIN, 0.04 [4]	49	5.00		$p \leq 0.001$

CPA: Cyclophosphamide; MN: Micronucleated; MMC: Mitomycin C; NS: Not significant; VIN: Vinblastine

1 Based on replication index

2 95th percentile of the observed range

3 Vehicle control was purified water

4 Positive control

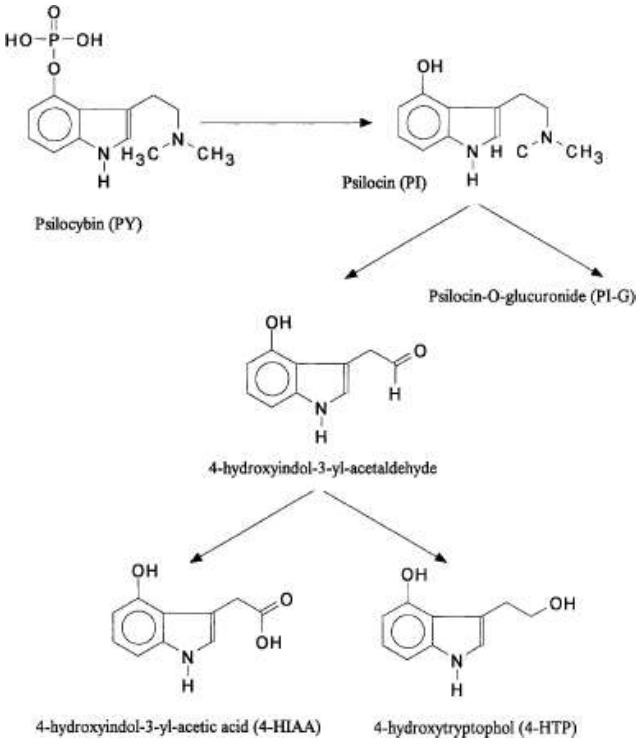
5. EFFECTS IN HUMANS

5.1. Pharmacokinetics and Metabolism in Humans

Following oral administration (0.224 mg/kg) of psilocybin, average blood concentration of the active metabolite psilocin was calculated to be 8.2 ± 2.8 ng/mL after 105 ± 37 minutes, yielding an estimated dose-normalized bioavailability of psilocybin to be 52.7 ± 20% (N = 3). Psilocin typically appears in plasma within 15 minutes after oral administration. Psilocin half-life following oral administration of psilocybin was found to be approximately 3 ± 1.1 hours, and is detectable for up to 24 hours after administration (Brown et al., 2017; Hasler, Bourquin, Brenneisen, Bar, & Vollenweider, 1997). The levels of psilocin peaked at approximately 80 minutes, but the peak psilocin concentration was more gradually attained in some subjects than in others, suggesting metabolism rates can vary between individuals (Brown et al., 2017).

Psilocin is metabolized to 4-hydroxyindole-3-acetic acid by deamination and demethylation via liver enzymes such as monoamine oxidase, and aldehyde dehydrogenase (Figure 5.1-1) (Hasler, Bourquin, Brenneisen, Bär, et al., 1997). Psilocin is also extensively glucuronidated by the UDP-glucuronosyltransferase (UGT) family of enzymes, with the highest glucuronidation activity demonstrated by UGT1A10 (Manevski et al., 2010). The amount of psilocin glucuronide-excreted renally has been shown to exceed that of psilocin over a 24-hr time period, and analysis of psilocin in urine over 24 hours after a single dose has shown that less than 4% of the overall clearance of psilocin occurs through renal excretion (Hasler, Bourquin, Brenneisen, & Vollenweider, 2002). The pharmacokinetics of psilocybin (as psilocin) are linear over the dose range of 0.3 – 0.6 mg/kg (Brown et al., 2017; Hasler et al., 2002).

Figure 5.1-1: Metabolism of psilocybin.



5.2. Human Pharmacology

Studies using positron emission tomography (PET) showed that psilocybin ingestion (15 or 20 mg orally) increased absolute metabolic rate of glucose in frontal, and to a lesser extent in other, cortical regions as well as in striatal and limbic subcortical structures in healthy participants, suggesting that some of the key behavioral effects of psilocybin involve the frontal cortex (Gouzoulis-Mayfrank, Schreckenberger, et al., 1999; Vollenweider & Geyer, 2001; Vollenweider et al., 1997). Although classic psychedelics, including psilocybin, vary in their specific repertoires of receptor binding affinities across a range of receptor sites, these agents share in common agonism at the serotonin 5HT2A receptor site (Carhart-Harris et al., 2014; Nichols, 2016; Vollenweider & Kometer, 2010). Pre-treatment with the serotonin 5HT2A receptor antagonist ketanserin was found to block most of the experiential/emotional/psychedelic effects of psychedelic compounds in humans (including acute increases in positive mood) (Kometer et al., 2012; Vollenweider, Vollenweider-Scherpenhuyzen, Babler, Vogel, & Hell, 1998). 5HT2A receptor stimulation depolarizes layer 5 pyramidal neurons leading to an increased firing rate (Aghajanian & Marek, 1997; Andrade, 2011). This increased firing in prefrontal cortex results in increased glutamatergic recurrent network activity, which can be abolished not only by 5HT2A receptor antagonists, but by also antagonists of several glutamate receptors, including the AMPA (alpha-amino-3-hydroxyl-5-methyl-4-isoxazole- propionic acid) receptor, that are increasingly implicated in the pathophysiology of depression (Maeng & Zarate, 2007).

Recent evidence suggests that psychedelic agonists have distinct biological effects not found in non-psychedelic 5HT2A agonists. Psychedelic, but not non-psychedelic, 5HT2A agonists have been shown via receptor-receptor interactions to enhance signaling through the dopamine D2 receptor in ventral striatum, which is of significant interest given that increased dopamine activity in this area correlates with euphoria in response to psilocybin (Vollenweider, Vontobel, Hell, & Leenders, 1999), and given that abnormalities in the D2 receptor have been reported in the same brain area in patients with major depression (Pei et al., 2010). Recent studies indicate that psychedelic and non- psychedelic 5HT2A agonists also differentially regulate intracellular signaling pathways in pyramidal neurons, with resultant differences in the expression of downstream signaling proteins, such as beta-arrestin 2 and early growth response protein 1 (EGR1) (Gonzalez-Maeso et al., 2007; Schmid, Raehal, & Bohn, 2008). Although 5HT2A agonism is widely recognized as the primary action of classic psychedelic agents, psilocybin has lesser affinity for a wide range of other pre- and post-synaptic serotonin and dopamine receptors, as well as the serotonin reuptake transporter (Tylš, Palenicek, & Horacek, 2014). Psilocybin activates 5HT1A receptors, which may contribute to antidepressant/anti-anxiety effects.

5.3. Clinical Trial Summaries

5.3.1. Introduction

Clinical trials examining the safety and preliminary efficacy of oral psilocybin administration in conjunction with cognitive enhancement therapy have been completed in the academic setting and are summarized in this section. These trials, enrolling 275 adult participants, include open-label, dose-escalating studies, as well as randomized, double-blind trials, and enrolled both healthy volunteers and various subpopulations with differing indications (Table 5.3-1).

Of the 275 participants enrolled across these studies, 264 received at least one dose of oral psilocybin, 180 participants received two doses, 71 participants received three doses, and 14 participants received four doses (study dosing schedules varied and are described in the sections below). In total, 529 oral psilocybin doses were administered. Doses ranged from "very low dose" (45 µg/kg) through "high dose" (600 µg/kg; 0.6 mg/kg).

One study (Imperial College of London) utilized a 25 mg dose. Six other studies and one retrospective analysis used within a range of 300 µg/kg – 315 µg/kg, which by body weight of participants closely resembles a 25 mg dose on average. Of these studies using either a 25 mg dose or 300-315 µg/kg range dose, 182 oral psilocybin doses were administered. Of these eight studies, six were dose-escalating studies and two were placebo-controlled studies. Of the dose-escalating studies, the 25 mg or 300-315 µg/kg dose was the highest dose in three, and the lowest dose in three.

Table 5.3-1: Summary of completed clinical trials studying oral psilocybin

Study	Reference	Study Design	Objective	Enroll-ment	Population	Dose
University of Wisconsin	Brown et al; *Clinical Pharmacokinetics*, 2017	Open-label, dose-escalating	Determine PK of an oral formulation of psilocybin in normal, healthy adults	12	Healthy adults	0.3, 0.45, 0.6 mg/kg (oral, dose escalating, every four weeks)
University of Zurich	Studerus et al; *J Psychopharmacol*, 2011	Retrospective analysis	Analyze acute, short- and long-term subjective effects of psilocybin in healthy humans from previously conducted double-blind, placebo- controlled experimental studies	110	Healthy adults	1-4 doses of oral psilocybin (45-315 µg/kg)
University of Arizona	Moreno et al; *J Clin Psychiatry*, 2006	Open-label, dose-escalating, proof of concept	Explore safety for human consumption of 4 doses of psilocybin in a small sample of symptomatic Obsessive Compulsive Disorder patients	9	Adults with Obsessive Compulsive Disorder	Oral psilocybin, 1x 100 µg/kg (low dose), 1x 200 µg/kg (medium dose) and 1x 300 µg/kg (high dose) sequentially, with 1x 25 µg/kg (very low dose) inserted randomly
University of New Mexico	Bogenschutz et al; *J Psychopharmacol*, 2015	Single-group, dose-escalating proof of concept study	Quantify acute effects of psilocybin in alcohol- dependent participants and provide preliminary outcome and safety data	10	Adults with active alcohol dependence	Oral psilocybin, 1x 0.3 mg/kg, and 1x 0.3 or 0.4 mg/kg four weeks apart
Johns Hopkins (Tobacco)	Johnson et al; *J Psychopharmacol*, 2014	Open-label, dose-escalating	Determine the safety and feasibility of psilocybin as an adjunct to tobacco smoking cessation treatment.	15	Psychiatrically healthy, nicotine-dependent adult smokers	Oral psilocybin, 1x 20 mg/70 kg (low dose). 1x 30 mg/70 kg (high dose), and 1x optional dosing (low or high)

Study	Reference	Study Design	Objective	Enrollment	Population	Dose
Imperial College of London	Carhart-Harris et al; *Lancet Psych*, 2016 and Carhart-Harris et al; *Psychopharmacol*, 2018	Open-label, dose-escalating feasibility study	Determine safety and efficacy outcomes for up to 6 months in an open-label trial of psilocybin for treatment-resistant depression	20	Adults with moderate or severe depression	Oral psilocybin, 1x 10 mg (low dose), 1x 25 mg (high dose) one week apart
Harbor-UCLA	Grob et al; *Arch Gen Psychiatry*, 2011	Randomized, double- blind, placebo-controlled, crossover	Evaluate efficacy of psilocybin for advanced- stage cancer patients	12	Adults with advanced cancer (various types)	0.2 mg/kg (1x oral psilocybin, 1x oral placebo)
Johns Hopkins	Griffiths et al; *J Psychopharmacol*, 2016	Randomized, double- blind, crossover	Investigate the effects of psilocybin dose (low vs high dose) on a variety of outcome measures relevant to anxiety or depressive disorders exacerbated by cancer diagnosis	56	Adult cancer patients	Oral psilocybin, 1x 0.014 mg/kg or 0.042 mg/kg (low dose) / 1x 0.31 mg/kg or 0.43 mg/kg (high dose)
NYU	Ross et al; *J Psychopharmacol*, 2016	Randomized, double- blind, placebo-controlled, crossover	Investigate the efficacy of a single psilocybin dosing session versus placebo (in conjunction with psychotherapy) to treat clinically significant anxiety or depression	31	Adults with cancer diagnosis	0.3 mg/kg oral psilocybin or 250 mg oral placebo

5.3.2. Safety and Pharmacokinetics Clinical Trials

5.3.2.1. University of Wisconsin Study

This single-site, open-label, dose-escalating clinical trial evaluated the pharmacokinetics of an oral formulation of psilocybin in normal, healthy adults (Brown et al., 2017). This study was performed to describe the pharmacokinetics and safety profile of psilocybin in sequential, escalating oral doses of 0.3, 0.45, and 0.6 mg/kg in 12 healthy adults. These participants had a mean weight of 78.1 kg, with a range of 60.9-119.8 kg. The mean doses for each dosing level, as defined by the average participant weight, would be 23.4 mg (0.3 mg/kg), 35.1 mg (0.45 mg/kg), and 46.9 mg oral psilocybin (0.6 mg/kg). The mean dose at the 0.3 mg/kg level, which was the lowest dose tested in this study, would be similar to a 25 mg oral psilocybin dose. Dosing was administered a minimum of four weeks apart, and subjects were monitored and observed for a 24-hour period with the time of dosing as the starting point. Assessments included blood pressure, heart rate and temperature measurements at pre-dose, 15, 30, 45, 60, 90, 120 minutes, and three, four, six eight, 12, 18, and 24 hours post-dose.

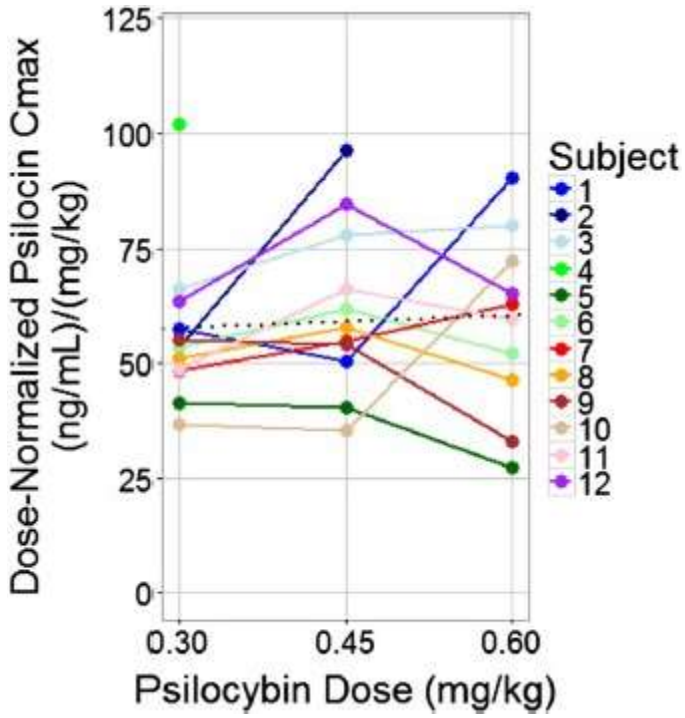
5.3.2.1.1. Results

Twelve subjects who met the inclusion/exclusion criteria were enrolled in this study. One subject was removed from the study and replaced because no blood samples could be obtained from the indwelling catheter or venipuncture at any time-point after the first dose. One subject received only one of the three planned doses due to hypertension unrelated to the investigational product. A third subject received only two doses of psilocybin due to an inability to continue participation unrelated to the investigational product. A total of 33 of 36 planned doses were administered.

5.3.2.1.2. Pharmacokinetics

Anticoagulated blood samples were collected at the time points mentioned above, and urine was collected for 24 hours after each dose. Psilocybin, as its active metabolite psilocin, demonstrated linear pharmacokinetics over the dose range tested, as indicated by the noncompartmental evaluation of dose-normalized area under the curve and C_{max}. The mean maximal concentration of psilocin increased in a dose proportional manner from 0.3 mg/kg psilocybin (16 µg/L), to 0.45 mg/kg (26 µg/L), to 0.6 mg/kg (37.6 µg/L). The dose-adjusted maximum concentration changed from 0.7 µg/L (0.3 mg/kg), to 0.838 µg/L (0.45 mg/kg), to 0.799 µg/L (0.6 mg/kg), and the time to reach C_{max} was between 2.03-2.05 hours for each dose level (Figure 5.3-1). Less than 5% of the oral psilocybin dose was excreted in urine as psilocin.

Figure 5.3-1: Dose-normalized plasma psilocin Cmax. The dotted black line represents the least squares regression.



5.3.2.1.3. Adverse Events

In general, all three dose strengths were physically and psychologically well tolerated, and no serious physical or psychological adverse events (AEs) occurring during or within 30 days of any dose were reported. The most frequently occurring AEs related to IP were mild hypertension (N = 22, 83% of participants), mild bradycardia (N = 22, 58%), mild headache (N = 14, 75%), and mild tachycardia (N = 12, 50%) (Table 5.3-2). Five moderate episodes of hypertension (33% of participants) were reported. Dose strength was not found to correlate to adverse event frequency. Elevations in blood pressure were transient and typically resolved within 8 hours. Ten of 14 (71%) headache AEs were resolved with acetaminophen (650 mg). Other available medications were not used (lorazepam, diazepam, nitroglycerin, carvedilol and IM haloperidol) *(Personal communication, Paul Hutson, PharmD).*

All expected and unexpected adverse events occurring from the time of enrollment into the study through the 30-day visit following the last dose were recorded. Severity of the AEs was graded by the Common Terminology Criteria for Adverse Events (CTCAE) version 4 criteria.

Table 5.3-2: Summary of adverse events related to psilocybin dosing*

Adverse Event Description†	Total No. of episodes	# of participants	# per dose		
			0.3mg/kg	0.45mg/kg	0.60mg/kg
hypertension (mild)	22	10/12 (83%)	8	8	6
hypertension (moderate)	5	4/12 (33%)	2	2	1
hypotension (mild)	1	1/12 (8%)	0	0	1
bradycardia (mild)	22	7/12 (58%)	8	7	7
tachycardia (mild)	12	6/12 (50%)	5	1	4
headache (mild)	14	9/12 (75%)	5	5	4
fever (mild)	6	5/12 (42%)	0	1	5
fatigue (mild)	5	4/12 (33%)	1	1	3
nausea (mild)	4	3/12 (25%)	2	2	0
diarrhea (mild)	1	1/12 (8%)	0	0	1
dizziness (mild)	1	1/12 (8%)	0	0	1

* Data is unpublished, and was obtained via personal communication from the study investigators

† AEs were reported within 24 hrs of dosing. Mild hypertension was defined as SBP 140 to 159 mm Hg or DBP 90 to 99 mm Hg; moderate hypertension was defined as SBP ≥160 mmHg or DBP ≥100 mm Hg; mild hypotension was defined as SBP <90 mm Hg over DBP <60 mm Hg, bradycardia was defined as <60 BPM; tachycardia was defined as > 100 BPM, mild fever was defined as $<39.0^0$ C.

5.3.2.1.4. Conclusion

Psilocybin was well tolerated in this study, and the PK parameters were found to be linear across a series of escalating doses.

5.3.2.2. University of Zurich

This was a retrospective analysis to analyze acute, short- and long-term subjective effects of psilocybin in healthy humans from eight previously conducted double-blind, placebo-controlled experimental trials (Table 5.3-3) (Studerus et al., 2011). Oral psilocybin was provided in either a single dose, or a range of up to four doses per participant, with dosing strength varying from 45 to 315 µg/kg. All studies were performed in a single laboratory over the course of 10 years, and analyzed the acute and persisting effects of 228 psilocybin sessions in 110 healthy volunteers. For dose- escalation studies, doses were randomized and separated by at least 14 days, and each volunteer received placebo in addition to oral psilocybin.

Table 5.3-3: Studies involving oral psilocybin dosing

Study description	Psilocybin dose conditions	Number of subjects receiving at least one dose of psilocybin	Very low dose (45 µg/kg)	Low dose (115–125 µg/kg)	Medium dose (115–260 µg/kg)	High dose (315 µg/kg)
1. Dose–effect study on acute psychological and physiological effects of psilocybin.	1) 45 µg/kg 2) 115 µg/kg 3) 215 µg/kg 4) 315 µg/kg	8	8	8	8	8
2. Acute effects of psilocybin on cognitive functions and subjective experience.	1) 115 µg/kg 2) 215 µg/kg 3) 315 µg/kg	16	-	16	16	16
3. Effects of psilocybin on brain activity using H2O-PET	260 µg/kg	12	-	-	12	-
4. Effects of psilocybin on prepulse inhibition of startle in healthy human volunteers.	1) 115 µg/kg 2) 215 µg/kg 3) 315 µg/kg	20	-	17	17	18
5. Effects of psilocybin on the rate and rhythmicity of perceptual rivalry alternations.	1) 115 µg/kg 2) 250 µg/kg	12	-	12	12	-
6. Investigation on the relationship between attention, working memory, and the serotonin 1A and 2A receptors using psilocybin and ketanserin	1) 215 µg/kg 2) 215 µg/kg after ketanserin pretreatment	10	-	-	10	-
7. Effects of psilocybin on visual processing: An EEG study	1) 125 µg/kg 2) 250 µg/kg	21	-	21	18	-
8. Serotonin 5-HT2A receptor dynamics in the human brain following psilocybin stimulation: A PET study.	250 µg/kg	11	-	-	11	-
Total number of subjects	-	*110*	8	74	104	42

5.3.2.2.1. Adverse Events

Psilocybin was generally well tolerated. There were no serious adverse events (SAEs) reported. The most frequent self-reported adverse experiences were mild headache and mild lethargy (fatigue, exhaustion, or lack of energy) immediately after psilocybin administration. For these events, normal function was largely restored after 24 hours. Complaints were reported 24 hours post-dose as per by the List of Complaints questionnaire. Table 5.3-4 shows the complete list of participant complaints, differentiated by dose effect relation versus placebo, and medium dose comparison to placebo.

Table 5.3-4: List of complaints 24 hours post-dose

	Dose effect relation (N = 40)						Medium Do (N	
Complaints	**Placebo**	**115 µg/kg**	**215 µg/kg**	**315 µg/kg**	***p*-value**	**Signif.**	**Placebo**	**215-250 µg/kg**
Fatigue	12.5% (5)	40.0% (16)	35.0% (14)	60.0% (24)	<0.001	***	19.4% (14)	40.3% (29)
Exhaustion	7.5% (3)	22.5% (9)	22.5% (9)	22.5% (9)	0.090		9.7% (7)	27.8% (20)
Headaches, head pressure or face pain	2.5% (1)	12.5% (5)	22.5% (9)	37.5% (15)	<0.001	***	8.3% (6)	19.4% (14)
Lack of energy	0.0% (0)	15.0% (6)	7.5% (3)	22.5% (9)	0.002	**	4.2% (3)	16.7% (12)
Excessive sleep requirement	2.5% (1)	10.0% (4)	10.0% (4)	15.0% (6)	0.177		6.9% (5)	12.5% (9)
Difficulty concentrating	5.0% (2)	7.5% (3)	7.5% (3)	17.5% (7)	0.015	*	4.2% (3)	13.9% (10)
Gone feeling	2.5% (1)	10.0% (4)	5.0% (2)	22.5% (9)	0.005	**	2.8% (2)	12.5% (9)
Fast exhaustibility	2.5% (1)	12.5% (5)	10.0% (4)	17.5% (7)	0.064		4.2% (3)	8.3% (6)
Brooding	5.0% (2)	5.0% (2)	0.0% (0)	12.5% (5)	0.106		4.2% (3)	12.5% (9)
Lack of appetite	0.0% (0)	7.5% (3)	5.0% (2)	17.5% (7)	0.015	*	1.4% (1)	9.7% (7)
Neck or shoulder pain	7.5% (3)	7.5% (3)	2.5% (1)	5.0% (2)	0.629		4.2% (3)	8.3% (6)
Irritability	5.0% (2)	10.0% (4)	5.0% (2)	7.5% (3)	0.768		2.8% (2)	5.6% (4)
Sexually stimulating fantasies	5.0% (2)	2.5% (1)	5.0% (2)	5.0% (2)	0.801		6.9% (5)	5.6% (4)
Strong thirst	2.5% (1)	5.0% (2)	5.0% (2)	0.0% (0)	0.468		1.4% (1)	9.7% (7)
Heavy or tired legs	2.5% (1)	0.0% (0)	2.5% (1)	12.5% (5)	0.008	**	2.8% (2)	4.2% (3)
Sleeplessness	2.5% (1)	0.0% (0)	7.5% (3)	5.0% (2)	0.290		1.4% (1)	6.9% (5)
Bloated feeling	5.0% (2)	0.0% (0)	5.0% (2)	2.5% (1)	0.300		2.8% (2)	5.6% (4)
Backache	2.5% (1)	5.0% (2)	2.5% (1)	2.5% (1)	0.896		2.8% (2)	5.6% (4)
Worries about professional or private affairs	0.0% (0)	5.0% (2)	2.5% (1)	5.0% (2)	0.532		4.2% (3)	4.2% (3)
Dark thoughts	5.0% (2)	5.0% (2)	2.5% (1)	2.5% (1)	0.801		4.2% (3)	2.8% (2)
Inner tension	2.5% (1)	7.5% (3)	0.0% (0)	7.5% (3)	0.234		1.4% (1)	2.8% (2)
Abdominal pain or stomach ache	2.5% (1)	2.5% (1)	2.5% (1)	7.5% (3)	0.392		1.4% (1)	2.8% (2)

	Dose effect relation (N = 40)						Medium Do (N	
Complaints	**Placebo**	**115 µg/kg**	**215 µg/kg**	**315 µg/kg**	***p*-value**	**Signif.**	**Placebo**	**215-250 µg/kg**
Intolerances to certain smells	0.0% (0)	2.5% (1)	2.5% (1)	5.0% (2)	0.494		1.4% (1)	5.6% (4)
Nausea	0.0% (0)	7.5% (3)	5.0% (2)	2.5% (1)	0.232		0.0% (0)	4.2% (3)
Uneasiness	2.5% (1)	2.5% (1)	2.5% (1)	5.0% (2)	0.875		1.4% (1)	2.8% (2)
Tendency of crying	2.5% (1)	0.0% (0)	2.5% (1)	0.0% (0)	0.572		1.4% (1)	5.6% (4)
Joint aches	2.5% (1)	2.5% (1)	2.5% (1)	0.0% (0)	0.733		1.4% (1)	4.2% (3)
Cold feet	2.5% (1)	0.0% (0)	2.5% (1)	2.5% (1)	0.801		1.4% (1)	4.2% (3)
Freezing	0.0% (0)	2.5% (1)	5.0% (2)	0.0% (0)	0.300		1.4% (1)	4.2% (3)
Ravenous appetite	5.0% (2)	2.5% (1)	2.5% (1)	0.0% (0)	0.494		2.8% (2)	1.4% (1)
Throat pain or irritated throat	5.0% (2)	0.0% (0)	0.0% (0)	7.5% (3)	0.101		2.8% (2)	0.0% (0)
Easy rubescence	2.5% (1)	7.5% (3)	0.0% (0)	0.0% (0)	0.066		2.8% (2)	0.0% (0)
Lump in throat or throat tightness	2.5% (1)	2.5% (1)	2.5% (1)	0.0% (0)	0.733		1.4% (1)	1.4% (1)
Diarrhea	2.5% (1)	0.0% (0)	0.0% (0)	7.5% (3)	0.112		1.4% (1)	0.0% (0)
Restless legs	5.0% (2)	2.5% (1)	0.0% (0)	0.0% (0)	0.300		2.8% (2)	0.0% (0)
Cold intolerance	0.0% (0)	2.5% (1)	2.5% (1)	0.0% (0)	0.392		0.0% (0)	4.2% (3)
Vertigo	2.5% (1)	0.0% (0)	0.0% (0)	2.5% (1)	0.392		2.8% (2)	1.4% (1)
Forgetfulness	0.0% (0)	0.0% (0)	2.5% (1)	5.0% (2)	0.194		0.0% (0)	2.8% (2)
Difficulty swallowing	2.5% (1)	0.0% (0)	0.0% (0)	5.0% (2)	0.300		1.4% (1)	0.0% (0)
Frequent urges to urinate	2.5% (1)	0.0% (0)	2.5% (1)	0.0% (0)	0.572		1.4% (1)	1.4% (1)
Strong perspiration	2.5% (1)	2.5% (1)	0.0% (0)	0.0% (0)	0.572		1.4% (1)	1.4% (1)

Numbers in parentheses indicate absolute frequencies. Dose effect relation population data is pooled from studies 1, 2 and 4 in Table 5 comparison population data is pooled from studies 1, 2, 4, 5, 6 and 8.

Five participants terminated their studies early. Three were withdrawn from their respective studies due to adverse events caused by psilocybin (two were removed by the investigator following an unusually intense reaction to low-dose psilocybin, and one subject was removed by the investigator after experiencing a transient hypotonic reaction with dizziness, fainting and vomiting after receiving low-dose psilocybin), and two voluntarily withdrew following administration of high-dose psilocybin due to symptoms of anxiety. In each case, symptoms were completely resolved by the end of the dosing day.

5.3.2.2.2. Abuse Potential

The large majority of participants (approximately 90%) reported "no change" in their psilocybin use following their laboratory sessions, as well as "no change" in their overall drug consumption habits (e.g., use of alcohol, nicotine, cannabis, MDMA). Those who did report changes often described decreased consumption. Specifically, in terms of psilocybin use, more participants reported using it less often after their laboratory sessions (5.6% of all participants) than more often (3.3% of all participants).

5.3.2.2.3. Conclusion

Collected data from the eight studies listed in Table 5.3-3 demonstrated that psilocybin was safe and well-tolerated under the conditions tested. Adverse events were generally classified as mild and resolved within 24 hours.

5.3.2.3. Additional Safety Results in Studies with Healthy Participants

The below studies present additional data related to monitoring of cardiovascular and psychological events. The first study not did actively monitor for participant-reported physical adverse outcomes, and the second checked only for a pre-determined subset of physical adverse events (yawning, nausea, spontaneous motor activity, and restlessness), as graded on a participant-reported scale from 0-4. The results are included for their relevance to acute cardiovascular and psychological outcomes.

5.3.2.3.1. Adverse Events

In a first study in 36 medically and psychiatrically healthy adults, a single dose of psilocybin (0.43 mg/kg) was compared to a methylphenidate placebo (Griffiths, Richards, McCann, & Jesse, 2006). In the group as a whole, psilocybin increased systolic BP by an average of 20 mm Hg and diastolic BP by an average of 12 mm Hg. Average heart rate increased by 10 beats per minute (BPM). No participants required pharmacological intervention for these cardiovascular effects. Eleven participants (31%) experienced significant anxiety and/or dysphoria during their psilocybin sessions, and six of these subjects (17% of the total) experienced transient episodes of paranoid ideation/ideas of reference, but none required pharmacological intervention. All acute effects resolved by the end of the psilocybin sessions.

In a second study, 18 medically- and psychiatrically-healthy adults were exposed to five sessions with dosages of 0 (placebo), 5, 10, 20, or 30 mg/kg, respectively, randomized to either an ascending or descending dose order (Griffiths et al., 2011). All physiological and psychological AEs showed a strong dose-response relationship, escalating as dosage increased. Mean peak systolic BP for the

escalating dosages was 132.6, 143.3, 145.7, 145.7, and 153.1 mm Hg, respectively. Mean peak diastolic BP were 77.5, 83.4, 83.9, 84.3, and 88.8 mm Hg respectively. The four maximal BP readings in the highest dose (0.43 mg/kg) condition were 187/84, 166/64, 182/88, and 178/95 mm Hg respectively. Mean maximal heart rate by dose was 74.8, 78.7, 77.9, 82.1, and 83.0 beats per minute, respectively. No pharmacological interventions were required for BP or heart rate elevations. Feelings of anxiety and fear, as well as paranoid ideation or ideas of reference also increased in frequency during the sessions as a function of increasing dose, being significantly more prominent at the highest dose (0.43 mg/kg) than the other doses. Overall, 39% of participants indicated they experienced extreme anxiety/fear at some time during the session.

Both of these studies included a 14-month follow-up, at which point no cases of hallucinogen persisting perception disorder (HPPD) were reported. No long-term AEs were identified in either study population. Follow-up interviews have found no evidence that participating in the study precipitated any abuse of psychoactive drugs, including alcohol (Garcia-Romeu, Griffiths, & Johnson, 2014).

5.3.3. Clinical Trials for Alternative Indications (OCD and Addiction)

5.3.3.1. University of Arizona Study

This open-label, dose-escalating proof of concept study explored safety for human consumption of four doses of oral psilocybin in nine adult participants with symptomatic obsessive compulsive disorder (OCD) (Moreno, Wiegand, Taitano, & Delgado, 2006). Escalation occurred sequentially with 100 µg/kg (low), 200 µg/kg (medium), and 300 µg/kg (high) oral doses, with a 25 µg/kg (very low) dose inserted randomly and in double-blind fashion any time after the first dose, with all doses occurring at least one week apart. Assessments included the Yale-Brown Obsessive Compulsive Scale (YBOCS) and visual analog scale (VAS) for OCD symptom severity, which were administered immediately before dosing, and at four, eight, and 24 hours post-dose.

5.3.3.1.1. Results

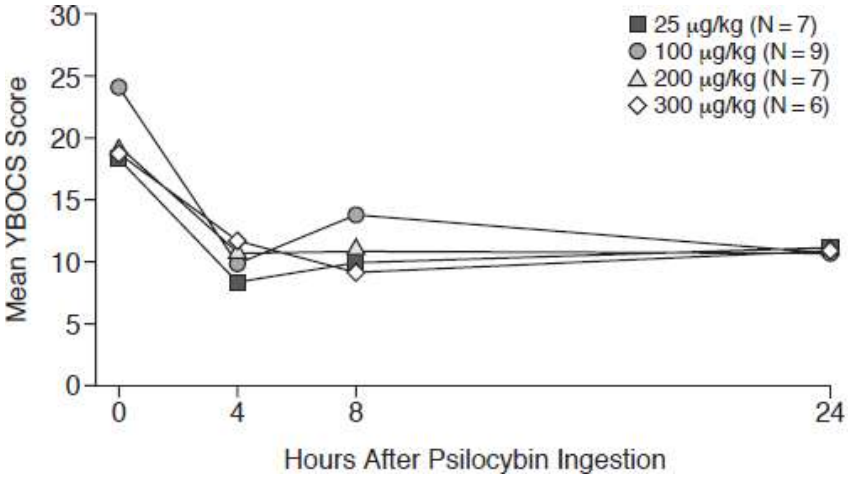
Nine participants (seven male, two female) meeting the inclusion criteria were administered a total of 29 oral psilocybin doses. All nine subjects received the low dose of psilocybin, seven also received the medium and very low doses, and six received all four doses. Two participants declined further participation unrelated to the study product following the low dose.

5.3.3.1.2. Clinical Efficacy

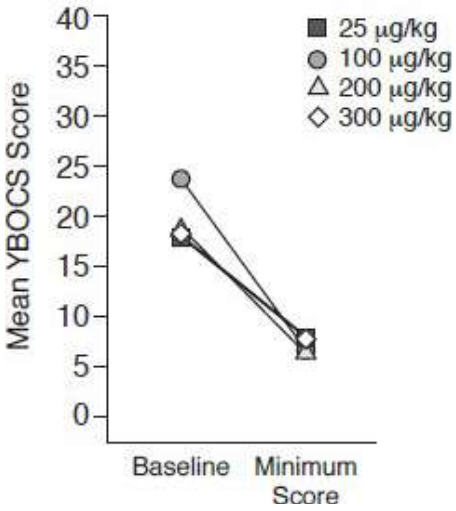
Decreases in OCD symptoms of a variable degree (23%-100%) were observed in all subjects during at least one dosing session per the YBOCS (Figure 5.3-2). Dose dependency on symptom reduction was not observed, with a decrease in average YBOCS score occurring after administration of each dose level (Figure 5.3-2).

Figure 5.3-2: Decreases in OCD scores as assessed by YBOCS. A) Mean YBOCS scores immediately prior to ingesting psilocybin through 24 hours after ingestion, and B) Average YBOCS scores prior to psilocybin ingestion as compared to the average of the lowest scores obtained (4, 8, or 24 hours) after ingestion, per dose.

A)



B)



5.3.3.1.3. Adverse Events

One participant experienced hypertension which was not associated with psychic anxiety or somatic symptoms. No other adverse reactions were observed.

5.3.3.1.4. Conclusion

Psilocybin was reported to be safe and well tolerated under the conditions tested at a series of four dosing levels, and was associated with acute reductions in core OCD symptoms in a population of adults with symptomatic OCD.

5.3.3.2. University of New Mexico Study

This was a single-group, dose-escalating proof of concept study to quantify the acute effects of oral psilocybin in 10 alcohol-dependent adult participants (four females), and provide preliminary outcome and safety data (Bogenschutz et al., 2015). Participants received a 12-week, 14-session manualized intervention including two open-label oral psilocybin sessions, the first after four weeks of psychosocial treatment (0.3 mg/kg), and the second after eight weeks (0.3 mg/kg or 0.4 mg/kg). Participants' vital signs were monitored at each visit at 30, 60, 90 and 120 minutes post-dose, and then hourly for an additional four hours. Psychological assessments were performed at subsequent follow-up visits, and cessation of drinking was monitored through 36 weeks.

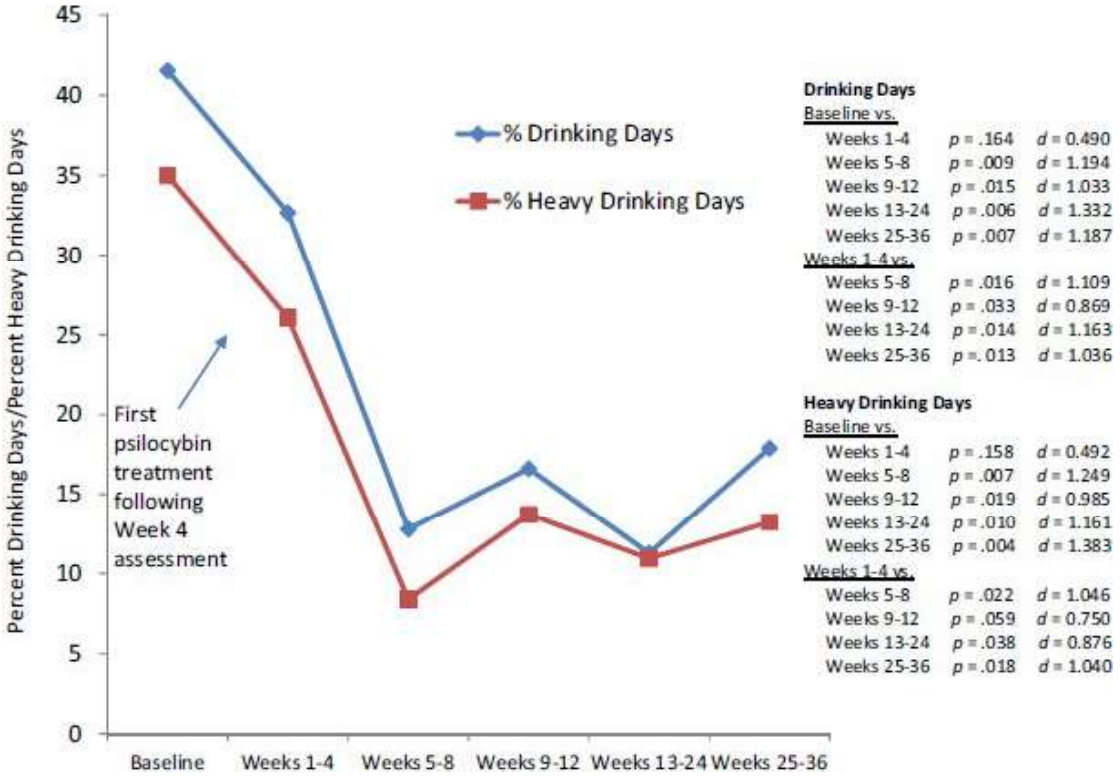
5.3.3.2.1. Results

All ten participants enrolled in the study completed the first oral psilocybin dosing at week 4 (0.3 mg/kg). Seven participants received the second psilocybin dose at week 8, with six receiving the increased dose (0.4 mg/kg). Three participants did not receive the second psilocybin dose. One withdrew participation, and two others did not receive treatment but completed all follow-up assessments. A total of 17 of 20 planned doses were administered.

5.3.3.2.2. Clinical Efficacy

Participants exhibited improvement in alcohol reliance after psilocybin dosing, and maintenance through 36 weeks (Figure 5.3-3). Mean percent of drinking days (days with any consumption of alcohol) decreased during weeks 5-12 relative to baseline (27.2 ± 23.7%; 95% CI 9.0-45.4, $p = 0.009$), and relative to weeks 1-4 (21.9 ± 21.8%; 95% CI 5.1-38.6, $p = 0.017$) prior to psilocybin administration. Mean percent of heavy drinking days (days where male participants consumed five or more drinks containing 14 g of alcohol, or female participants consumed four or more drinks containing 14 g of alcohol) also decreased during weeks 5-12 relative to baseline (26.0 ± 22.4; 95% CI 8.7-43.2, $p = 0.008$) and weeks 1-4 (18.2 ± 20.0%; 95% CI 2.8-33.5, $p = 0.026$).

Figure 5.3-3: Improvement in alcohol reliance following psilocybin treatment. Means shown for all available data (N=10 at baseline, N = 9 at all other time points).



5.3.3.2.3. Adverse Events

Adverse events were collected following psilocybin administration, and at all subsequent visits. The most common adverse event was mild headache (5 of 10 participants, 50%), which resolved within 24 hours following psilocybin administration. One participant (10%) reported nausea with one episode of emesis. One participant (10%) experienced diarrhea after psilocybin administration, though the participant had pre-existing irritable bowel syndrome. One participant (10%) reported insomnia on the night following psilocybin administration. Treatment or other intervention was not required for blood pressure, anxiety, or other psychiatric symptoms. No serious adverse events were reported.

5.3.3.2.4. Conclusion

Psilocybin administration was well-tolerated at the two dosing levels examined, and in conjunction with motivational enhancement therapy, increased alcohol abstinence in a population of participants with alcohol dependence when compared to baseline.

5.3.3.3. Johns Hopkins (Tobacco) Study

This was an open-label, dose-escalating study to determine the safety and feasibility of oral psilocybin as an adjunct to tobacco smoking cessation treatment in 15 psychiatrically healthy, nicotine-dependent adult smokers (five females) (M. W. Johnson, Garcia-Romeu, Cosimano, &

Griffiths, 2014). Oral psilocybin was administered at a low dose (20 mg/70 kg) and a high dose (30 mg/70 kg), with an option for a third dose (low or high), during a 15-week period coinciding with a structured smoking cessation cognitive behavioral therapy treatment protocol. Dosing occurred at weeks 5, 7, and 13 (optional). Participants were monitored through week 15, and then again during a six-month follow-up. Assessments included questionnaires, self-efficacy determinations, biomarker (breath carbon monoxide, urine cotinine) and safety data.

5.3.3.3.1. Results

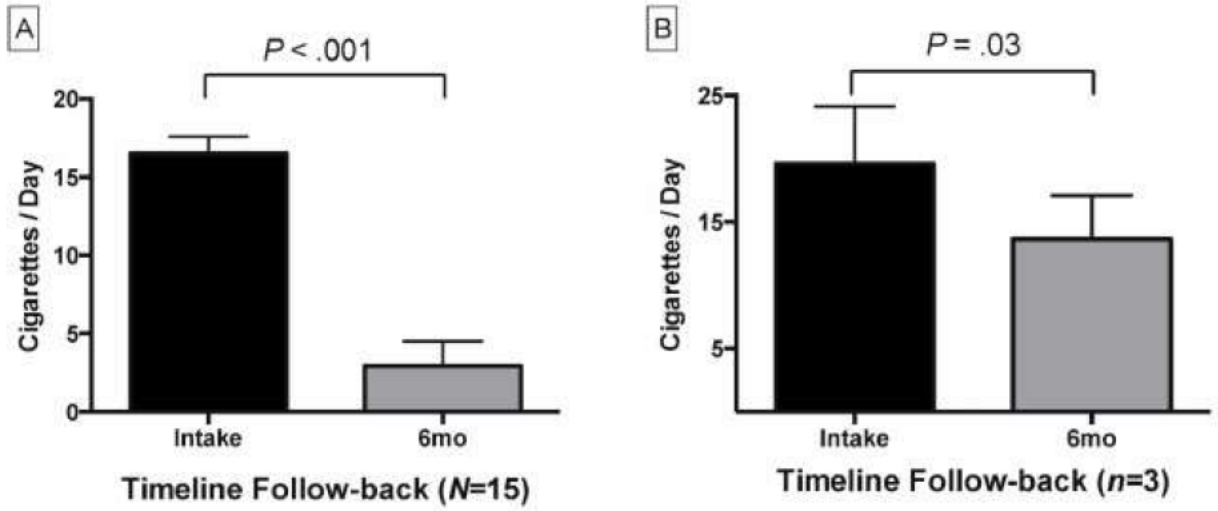
Fifteen participants completed the study, and 12 participants (80%) completed three doses of psilocybin. Three of 15 participants (20%) did not receive the third, optional dose. Amongst participants who received the optional dose, 11 of 12 (92%) opted for the high dose. 30 of 30 (100%) planned doses were administered, and 42 of 45 possible psilocybin sessions (93%) occurred under supportive conditions.

5.3.3.3.2. Clinical Efficacy

Twelve of 15 participants (80%) reported seven-day point prevalence abstinence at the six-month follow-up, and 11 (73%) were biologically confirmed to have quit smoking. Three participants (20%) tested positive for smoking at the six-month follow-up. On average, daily cigarette intake was reduced following psilocybin administration across the study population, as well as in the subpopulation (3 of 15) who tested positive for smoking at the six-month follow-up (Figure 5.3-4).

Figure 5.3-4: Timeline follow-back data for smoking cessation following psilocybin treatment.

Timeline follow-back data at the six-month time point for A) the entire study population, and B) the three participants who tested positive for smoking at the six-month follow-up.



5.3.3.3.3. Adverse Events

No serious adverse events were reported during the study. The most frequently reported adverse events included increases in blood pressure (BP) and heart rate (HR), post-treatment headache and

in-session episodes of anxiety. The number of increases in blood pressure was not explicitly reported, but across all sessions baseline values for mean maximal systolic BP increased from 125 ± 10 mm Hg to 153 ± 11 mm Hg, mean maximal diastolic BP increased from 71 ± 8 mm Hg to 87 ± 11 mm Hg, and mean maximal HR increased from 68 ± 9 to 87 ± 11 beats per minute following psilocybin administration. Ten of 15 subjects were assessed for headache following dosing (the initial five study participants did not receive post-session headache interviews), and eight (80%) reported headaches of mild severity on average (individual assessments not provided). Five of 10 (50%) reported use of over-the-counter medication to resolve the headache. Six participants (40%) had at least one episode (5 total episodes during low dose administration and 5 during high dose administration) of significant fear/anxiety during psilocybin sessions, with one (7%) self-reporting the event as extreme and five (33%) self-reporting the events as strong. With the exception of headaches, all acute adverse events had resolved by the end of the psilocybin sessions, and no pharmacological interventions were required.

5.3.3.3.4. Conclusion

Oral psilocybin was well tolerated under the conditions tested, and the authors considered the results of the study to support the feasibility of psilocybin with behavioral therapy as treatment for cessation of smoking.

5.3.4. Clinical Trials for Depression and Anxiety

5.3.4.1. Imperial College of London Study

This was an open-label, dose-escalating feasibility study to determine the safety and efficacy outcomes for up to six months post-dose of oral psilocybin in 20 adults (six females) with moderate (N = 2) or severe depression (N = 18) (Carhart-Harris et al., 2016). Participants received a low (10 mg) and high (25 mg) dose of oral psilocybin one week apart, with monitoring for six hours after dosing, and long-term follow-up through six months. Assessments included blood pressure, heart rate, and observer ratings of psilocybin's psychoactive effects at pre-dose, and 30, 60, 120, 180, 240, 300, and 360 minutes post-dose time points. Functional magnetic resonance imaging (fMRI) scanning also occurred the day after the second dose, and interim questionnaires were presented at Day 1, Week 1, Week 2, Week 3, Week 5, Month 3, and Month 6 after the second dose.

5.3.4.1.1. Results

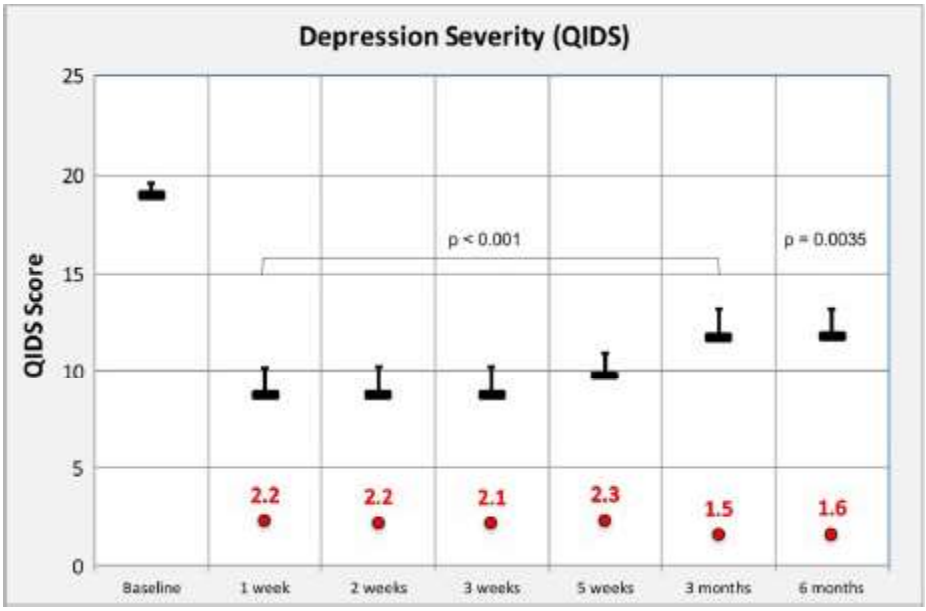
Nineteen of 20 participants completed assessments at all time points, and all participants completed both doses of oral psilocybin. One participant did not complete follow-up measures following his second dose.

5.3.4.1.2. Clinical Efficacy

The primary outcome measure of self-reported depression severity as gauged by the Quick Inventory of Depressive Symptomatology (QIDS) showed reductions relative to baseline QIDS scores, from one week to six months after high-dose psilocybin administration for the 19 participants who completed all assessments. Mean QIDS values were found to be below the threshold for reflection

of severe depression for each post-dose time point (Figure 5.3-5) (Carhart-Harris et al., 2016).

Figure 5.3-5: Mean QIDS values to assess self-reported depression. Mean values (black horizontal bars) as calculated for the 19 study completers, with error bars included. QIDS scores of 16-20 are considered to reflect severe depression. Cohen's d values vs baseline are shown in red, all contrasts vs baseline yielded p values of < 0.001 with the exception of the 6 month contrast which was p = 0.0035.



Score results relative to baseline for the additional study questionnaires are summarized in Table 5.3-5. Self-reported questionnaires gauged depression (Beck Depression Inventory; BDI), anxiety (State- Trait Anxiety Inventory; STAI), and anhedonia (Snaith-Hamilton Pleasure Scale; SHAPS). Clinician-administered ratings were collected to assess depression (Hamilton Depression Scale; HAM-D), and global functioning (Global Assessment of Functioning; GAF). Nine and four participants respectively met the criteria for response and remission at the week five time point, and reductions in depressive symptoms were observed through six months.

Table 5.3-5: Individual patient clinical rating results

	BDI				STAI				SHAPS			
	Baseline	**1 Week**	**3 Mos**	**6 Mos**	**Baseline**	**1 Week**	**3 Mos**	**6 Mos**	**Baseline**	**1 Week**	**3 Mos**	**Base**
Mean (*SD*)	34.5 *7.3*	*11.8* *11.1*	*19.2* *13.9*	*19.5* *13.9*	*68.6* *6.1*	*44.8* *15.7*	*56.5* *13.3*	*53.8* *13.3*	*6.6* *4.1*	*1.9* *2.7*	*3.3* *4.2*	*24.* *5.4*
Difference vs base-line (*SD*)	-	– *22.7* *10.6*	– *15.3* *13.7*	– *14.9* *12.0*	-	– *23.8* *15.2*	– *12.2* *12.7*	– *14.8* *14*	-	– *4.6* *4.1*	– *3.3* *4.6*	-
Cohen's d value	-	*2.5*	*1.4*	*1.4*	-	*2.2*	*1.2*	*1.5*	-	*1.3*	*0.8*	-
***p* value**	-	$p < 0.001$	$p < 0.001$	$p < 0.001$	-	$p < 0.001$	$p < 0.001$	$p < 0.001$	-	$p < 0.001$	$p = 0.005$	-

Clinician administered ratings (HAM-D and GAF) were completed at baseline and one week post-dosing only.

5.3.4.1.3. Adverse Events

The most common side effects reported were mild to moderate transient anxiety (N = 15; 79%), and mild to moderate headache (N = 8; 42%). Five participants (26%) reported transient nausea, but there were no cases of vomiting. Three participants (16%) reported transient paranoia within the duration of the acute drug experience. There were no serious adverse events reported.

5.3.4.1.4. Conclusion

Oral psilocybin was well tolerated under the conditions tested, and the depressive symptoms measured were seen to improve and remain improved for six months following the final study dose.

5.3.4.2. Harbor-UCLA Study

This was a randomized, double-blind, placebo-controlled crossover design study (NCT00302744) to evaluate the efficacy of psilocybin in 12 adults (11 females) with advanced-stage cancer (various types) and reactive anxiety (Grob et al., 2011). The dosing sessions were spaced several weeks apart, and participants would receive either oral psilocybin (0.2 mg/kg) or oral placebo (niacin, 250 mg) in a randomized order. Assessments included monitoring for temperature, heart rate and blood pressure, and dosing sessions concluded with self-reported participant outcomes. The duration of follow-up was six months following the second dosing session.

5.3.4.2.1. Results

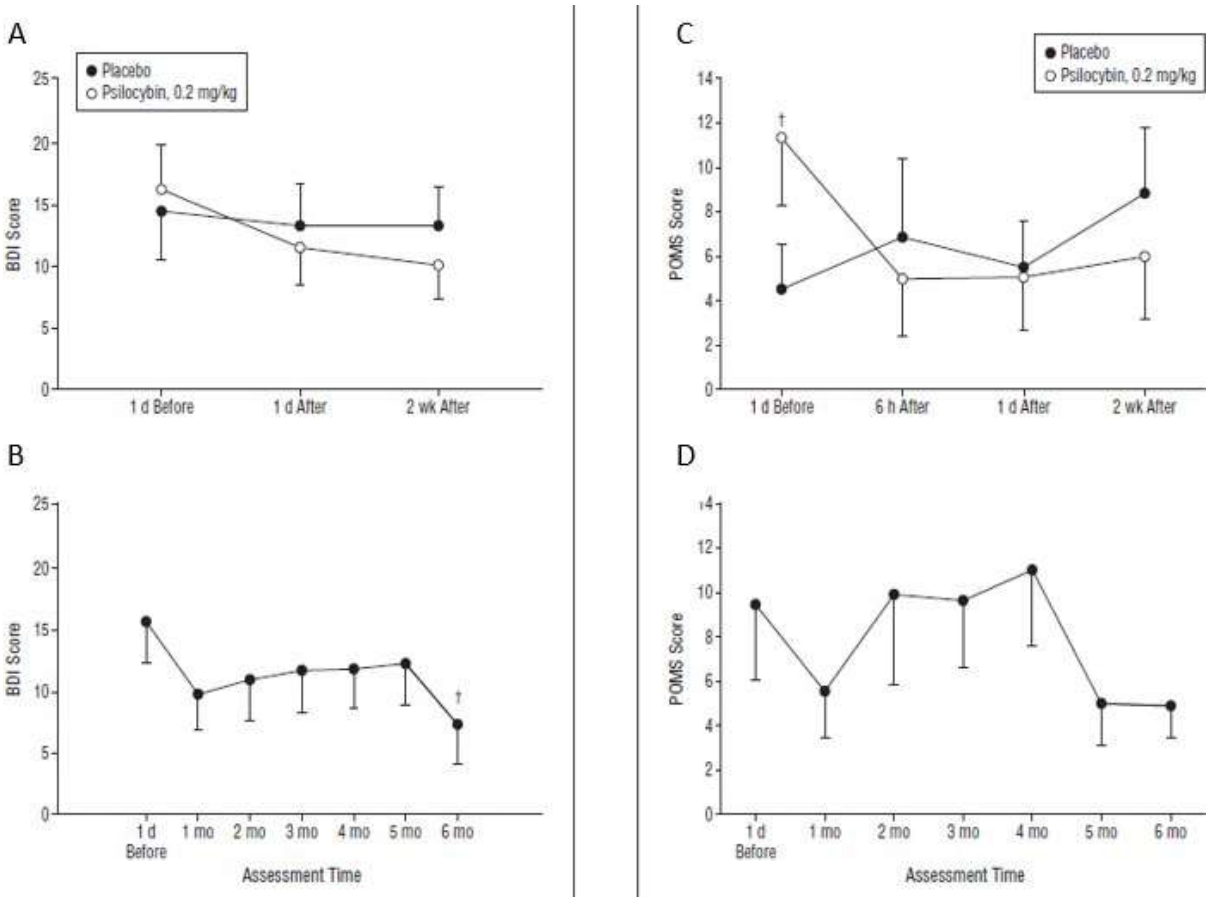
All 24 planned doses (12 psilocybin, and 12 placebo) were administered. Eight of 12 participants (67%) completed the 6-month follow-up assessment, 11 (92%) completed at least the first four months of assessment, and all 12 (100%) completed at least the first 3 months of follow-up. Two subjects died due to their underlying cancer during the follow-up period, and two others became too ill to continue participating.

5.3.4.2.2. Clinical Efficacy

As per the self-reported Beck Depression Inventory (BDI) scores for psilocybin through two weeks post-dose, there was an overall reaction that approached but did not attain statistical significance. There was no appreciable change in BDI scores for the placebo control (Figure 5.3-6A). Long-term follow-up through six months were sustained, dropping nearly 30% from pre-administration to month one, and achieving statistical significance at month six (P = 0.03).

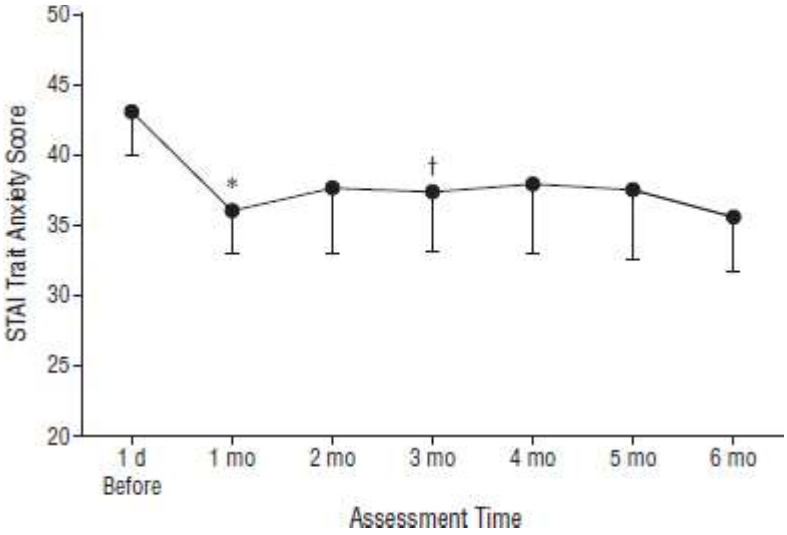
Self-reported Profile of Mood States (POMS) scores also revealed a trend for reduced adverse mood relative to placebo, with improvement of mood shown by 11 of 12 (92%) of participants after psilocybin dosing. It was noted though that mean POMS scores prior to dosing were elevated for psilocybin relative to placebo. There was no pattern observed for POMS scores during the six-month follow-up period (Figure 5.3-6).

Figure 5.3-6: BDI and POMS scores between placebo and psilocybin for assessment of clinical efficacy. A) Mean BDI scores between placebo and psilocybin for up to two weeks after administration. B) Mean BDI scores reported during the 6-month follow-up following the second dosing event. C) Mean POMS scores between placebo and psilocybin for up to two weeks after administration. D) Mean POMS scores during the 6-month follow-up following the second dosing event. N = 12 for all time points up to three months, N = 11 for the 4-month time point, and N = 8 for the Months 5 and 6 time points. †*P*_<0.05 for psilocybin vs the value from 1 day before the first treatment session (*t* tests were used to compare individual monthly follow-up values with values on the day before the first session).



Self-reported scores from the State-Trait Anxiety Index (STAI) did not yield significant change for the state anxiety subscale. A sustained decrease for the STAI trait anxiety subscore was shown through the duration of follow-up, achieving statistical significance at Months 1 and 3 (Figure 5.3-7).

Figure 5.3-7: STAI trait anxiety subscores through long-term follow-up. N = 12 for all time points up to three months, N = 11 for the 4-month time point, and N = 8 for the Months 5 and 6 time points. *P_<0.01, †P_<0.05 for psilocybin vs the value from 1 day before the first treatment session (t tests were used to compare individual monthly follow-up values with values on the day before the first session).



5.3.4.2.3. Adverse Events

No serious adverse events were reported during the study, and no adverse psychological effects arose from treatment (Grob et al., 2011). Adverse events were collected during study administration and solicited during monthly follow-up phone calls. No untoward cardiovascular sequelae was observed, though treatment with psilocybin produced transient increases in blood pressure (BP) and heart rate as compared to placebo. In response to psilocybin, mean maximum systolic BP increased from 117 ± 4.3 mm Hg to 138.9 ± 6.4 mm Hg, mean maximal diastolic BP increased 69.6 ± 2.7 mm Hg to 75.9 ± 3.4 mm Hg, and mean maximal heart rate increased from 70.4 ± 4.3 beats per minute to 81.5 ± (5.8) beats per minute. No additional information on adverse event reporting was available.

5.3.4.2.4. Conclusion

The study demonstrated that controlled use of psilocybin in advanced-stage cancer patients could provide an alternative model for treatment of anxiety and despair. Psilocybin was found to be well-tolerated, and no clinically significant adverse events were reported.

5.3.4.3. Johns Hopkins Study

This was a randomized, double-blind, crossover study (NCT00465595) to investigate the effects of psilocybin dose (low vs high dose) on a variety of outcome measures relevant to anxiety or depressive disorders exacerbated by cancer diagnosis (Griffiths et al., 2016). Participants were initially randomized to either the low dose oral psilocybin (0.014 mg/kg or 0.042 mg/kg), meant to act as placebo, or high dose oral psilocybin (0.31 mg/kg or 0.43 mg/kg), followed by crossover approximately five weeks later. The low dose was permanently adjusted to 0.014 mg/kg due to concern that a 0.042 mg/kg dose might not serve effectively as an inactive placebo, and the high

dose was similarly adjusted from 0.43 mg/kg to 0.31 mg/kg after two of the first three participants to receive the 0.43 mg/kg dose were discontinued from the study. Monitoring for adverse events occurred during dosing days up to six hours post-dose, and participant reported outcomes were solicited for up to six months following the second dose.

5.3.4.3.1. Results

Fifty-six participants meeting the inclusion and exclusion criteria were initially randomized to receive either the low dose (N = 27) or high dose (N = 29) oral psilocybin. Five subjects were removed from the study following randomization, with data not obtained for the first dosing session, including two in the low dose arm (one for pre-treatment anxiety and one for cancer progression), and three in the high dose arm (one for anxiety, one for vomiting shortly after capsule administration, and one for family reasons). Data were not obtained for an additional two participants, one in each randomization group, following crossover, due to progression of disease. Data following the initial dosing session were obtained from 51 participants (91%), 49 participants (88%) following the second dosing session, and six-month follow-up data was obtained for 46 participants (82%).

5.3.4.3.2. Clinical Efficacy

Therapeutically relevant measures describing mood, attitude, disposition and behavior were collected at baseline, approximately five weeks after each dosing session, and at six months following the second dosing session. Primary therapeutic outcomes included two clinician-rated measures: the GRID-Hamilton Depression Rating Scale (GRID-HAMD) for depression, and the Hamilton Anxiety Rating Scale (HAM-A) for anxiety. Secondary measures included self-rated questionnaires to examine depression, anxiety, mood, quality of life, and other psychosocial measures.

Both primary outcome measures, as well as most secondary measures, showed sustained effects following high-dose psilocybin treatment (either an effect from baseline to the first dose for the study arm starting with high-dose psilocybin, or an effect after the second dose for the study arm starting with low-dose psilocybin). Data for GRID-HAMD and HAM-A from baseline through the six-month follow-up time point, as well as the other statistically significant secondary measures, are provided in Table 5.3-6 and Figure 5.3-8. Numerical data in Table 5.3-6 show means (and standard error) for outcome measures in the two dose sequence groups: (1) those that received a low dose on the first session and a high dose on the second (N = 25, 25, 24, and 22 at Baseline, Post-session one, Post-session two, and six months, respectively), and (2) those that received a high dose on first session and a low dose on the second (N = 26, 25 or 26, 25, and 24 at Baseline, Post-session one, Post-session two, and six months, respectively). Data are shown for the 11 measures that fulfilled the most conservative criteria for demonstrating psilocybin effects.

Table 5.3-6: Effects of psilocybin on primary and select secondary outcome measure scores

Measure	Group	Assessment time-point			
		Baseline[a]	Post-session 1[b]	Post-session 2[c]	6 months[d]
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	22.32 (0.88)	14.80 (1.45)	6.50 (0.86)***	6.95 (1.24)
	High-Dose-1st (Low-Dose-2nd)	22.84 (0.97)	6.64 (1.04)***	6.52 (1.44)	6.23 (1.30)
Beck Depression Inventory	Low-Dose-1st (High-Dose-2nd)	18.40 (1.09)	12.92 (1.58)	8.17 (1.24)***	8.00 (1.50)
	High-Dose-1st (Low-Dose-2nd)	17.77 (1.61)	7.00 (1.39)**	5.80 (1.41)	6.17 (1.26)
HADS Depression	Low-Dose-1st (High-Dose-2nd)	9.48 (0.71)	6.04 (0.79)	4.57 (0.73)*	4.64 (0.72)
	High-Dose-1st (Low-Dose-2nd)	9.81 (0.69)	3.92 (0.74)*	4.28 (0.89)	3.46 (0.66)
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	25.68 (0.89)	16.64 (1.53)	8.92 (1.14)***	7.95 (1.19)
	High-Dose-1st (Low-Dose-2nd)	25.73 (1.11)	8.48 (1.16)***	7.52 (1.27)	7.04 (1.17)
STAI-Trait Anxiety	Low-Dose-1st (High-Dose-2nd)	47.46 (1.62)	40.48 (2.11)	35.48 (2.05)**	36.83 (2.08)
	High-Dose-1st (Low-Dose-2nd)	47.73 (1.91)	34.64 (1.84)*	34.28 (2.25)	35.32 (2.18)
POMS Total Mood	Low-Dose-1st (High-Dose-2nd)	51.72 (6.35)	42.48 (7.72)	21.09 (5.81)***	23.50 (6.57)
	High-Dose-1st (Low-Dose-2nd)	56.93 (5.33)	18.96 (5.78)**	17.14 (6.35)	12.52 (5.36)
Brief Symptom Inventory	Low-Dose-1st (High-Dose-2nd)	41.76 (4.40)	33.74 (4.47)	26.08 (4.53)*	23.50 (3.85)
	High-Dose-1st (Low-Dose-2nd)	40.19 (3.71)	18.08 (3.62)**	16.48 (3.77)	14.35 (3.35)
MQOL (Overall Quality of	Low-Dose-1st (High-Dose-2nd)	5.69 (0.24)	6.17 (0.32)	6.90 (0.34)**	6.88 (0.37)
	High-Dose-1st (Low-Dose-2nd)	5.32 (0.29)	7.14 (0.29)*	7.46 (0.34)	7.65 (0.36)
MQOL (Meaningful Existence)	Low-Dose-1st (High-Dose-2nd)	6.03 (0.30)	6.10 (0.39)	7.30 (0.35)***	7.29 (0.31)
	High-Dose-1st (Low-Dose-2nd)	5.43 (0.29)	7.23 (0.33)*	7.30 (0.38)	7.62 (0.35)
LAP-R Death Acceptance	Low-Dose-1st (High-Dose-2nd)	28.05 (2.04)	29.14 (2.25)	34.95 (1.92)***	34.95 (1.52)
	High-Dose-1st (Low-Dose-2nd)	29.09 (2.07)	36.17 (1.59)*	35.13 (1.90)	36.25 (1.59)
LOT-R (Optimism)	Low-Dose-1st (High-Dose-2nd)	13.56 (0.97)	13.60 (1.23)	15.96 (1.12)**	16.68 (1.14)
	High-Dose-1st (Low-Dose-2nd)	14.15 (0.97)	17.23 (0.67)*	17.16 (0.99)	17.43 (0.92)

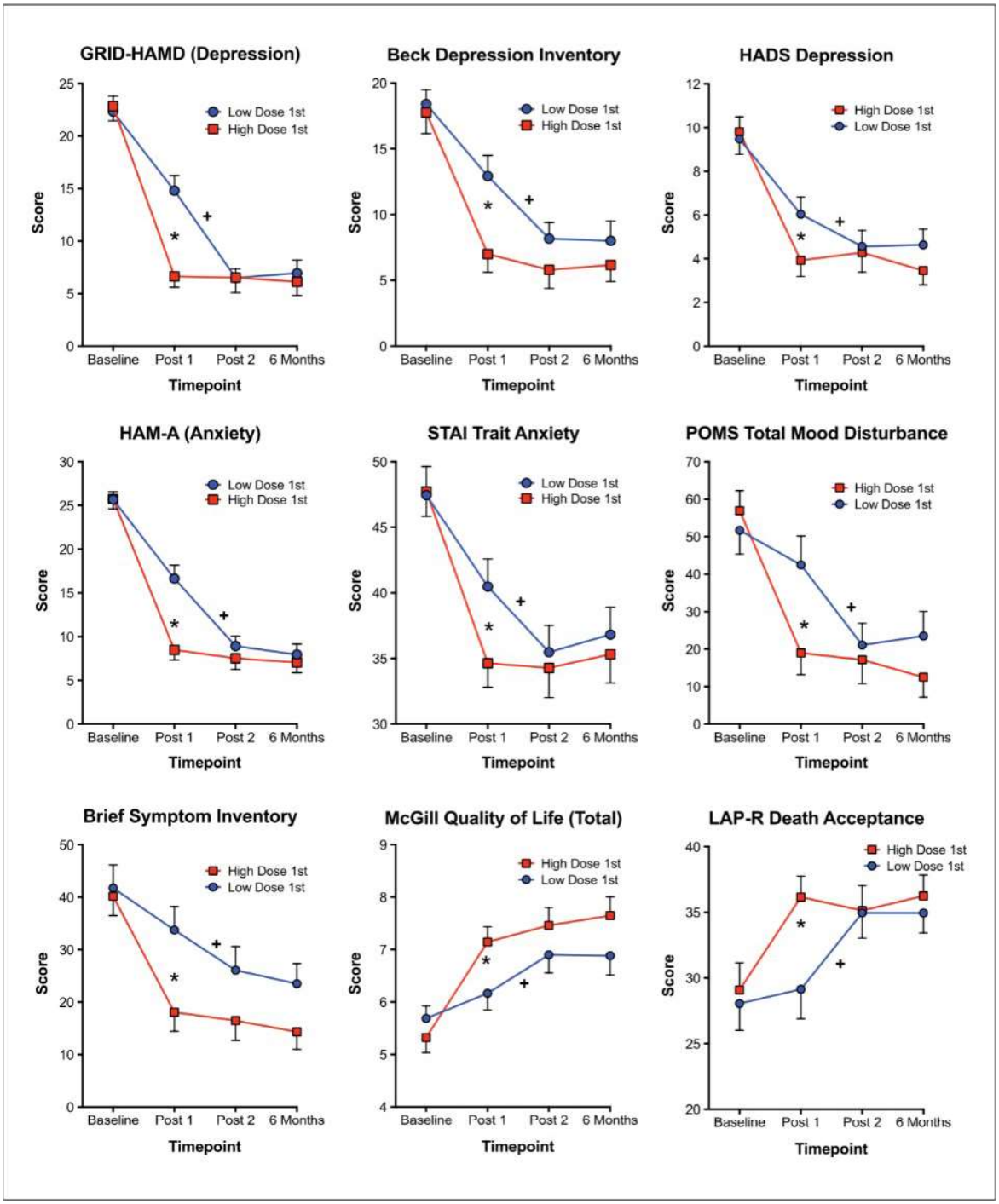
[a] In this column (Baseline), there were no significant differences between groups.

[b] In this column, italic font indicates a within-group significant difference from Baseline ($p<.05$, planned comparison); asterisks indicate significant differences between groups (*$p<0.05$, **$p<0.01$, ***$p<0.001$, planned comparisons); between groups effect size (Cohen's *d* as absolute values) for the 11 measures from top to bottom were: 1.30, 0.81, 0.56, 1.23, 0.60, 0.70, 0.78, 0.65, 0.65, 0.97, and 0.75.

[c] In this column, there were no significant differences between groups; asterisks indicate significant differences between the Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group (*$p<0.05$,**$p<0.01$, ***$p<0.001$, planned comparisons); effect size (Cohen's *d* as absolute values) for the 11 measures from top to bottom were: 1.33, 0.69, 0.40, 1.10, 0.50, 0.64, 0.35, 0.46, 0.66, 0.68, and 0.41.

[d] The difference between Baseline and 6 months, collapsed across groups, was significant for all 11 measures ($p<0.001$, planned comparison); effect size (Cohen's *d* as to bottom were: 2.98,1.63, 1.65, 3.40, 1.20, 1.26, 1.17, 1.14, 1.12, 0.84, and 0.66.

Figure 5.3-8: Outcome measures to assess clinical efficacy in the Johns Hopkins study. Data points show means; brackets indicate one standard error of the mean; circles represent the group that received a low dose on the first session and a high dose on the second session (N = 25, 25, 24, and 22 at Baseline, Post-session one, Post-session two, and six months, respectively); squares represent the group that received a high dose on first session and a low dose on the second session (N = 26, 26, 25, and 24 at Baseline, Post-session one, Post-session two, and six months, respectively). *Indicates a significant difference between the two groups at the Post-session one time-point ($p<0.05$, planned comparison). +Indicates a significant difference between the Post-session one and Post-session two time-points in the Low-Dose-first (High-Dose-second) Group ($p<0.05$, planned comparison).



Following the first post-dose assessment 92% of participants in the high-dose first group met standard criteria for depressive symptom clinical response and 60% met criteria for symptom remission as per the GRID-HAMD measure (p <0.001 and p = <0.01, respectively), compared with 32% and 16% respectively in the low-dose first group. In the high-dose first group 76% met criteria for anxiety symptom clinical response and 52% met criteria for symptom remission at first post-dose assessment as per the HAM-A measure (p <0.001 and p = <0.01, respectively), compared with 24% and 12% respectively in the low-dose first group. At the six-month assessment, by which time all participants were at least six months out from receiving a high-dose intervention, rates of response and remission remained high in both groups (high-dose first: depressive clinical response was 79% and symptom remission was 71%, and anxiety clinical response was 83% and symptom remission was 63%; low-dose first: depressive clinical response was 77% and symptom remission was 59%, and anxiety clinical response was 82% and symptom remission was 50%).

In addition to large-effect size reductions in depression and anxiety, high-dose psilocybin produced significantly greater ratings than low-dose psilocybin of positive persisting effects on attitudes about life and self, social effects, and spirituality. These effects were generally sustained at the six-month follow-up. Consistent with the positive changes, high-dose experiences (whether received at the first or second intervention) were also rated as producing significantly greater personal meaning, spiritual significance and increased well-being or life satisfaction than the low-dose experiences, with these improvements sustained at six months.

5.3.4.3.3. Adverse Events

No serious adverse events were attributed to psilocybin. The most frequent adverse events occurring during psilocybin dosing sessions (both low dose and high dose) are shown in Table 5.3-7. With the exception of headache, all adverse events had resolved fully by the end of the sessions. The most frequent adverse events were transient moderate increases in systolic and/or diastolic blood pressure (DBP) after psilocybin, psychological discomfort, anxiety, and physical discomfort. Episodes of elevated systolic blood pressure (>160 mm Hg) occurred in 18 of 53 (34%) high dose sessions, as compared to 17% (N = 9) of the low dose "placebo" sessions. Episodes of elevated diastolic blood pressure (>100 mm Hg) occurred in 7 of 53 (13%) high dose sessions, and 1 of 52 (2%) of the low dose sessions. One participant experienced a transient peak blood pressure (214/114 mm Hg) during the high dose session that met severity criteria, but not the duration (15 minutes) criteria for pharmacologic intervention, and therefore no intervention was delivered.

Psychological discomfort was reported in 17 of 53 (32%) of high dose sessions and 6 of 52 (12%) low dose sessions. Anxiety was reported in 14 of 53 (20%) of high dose sessions, and 8 of 52 (15%) low dose sessions. Episodes of physical discomfort (any type) occurred in 21% of high dose sessions and 8% of low dose sessions.

One instance of mild headache was reported during a high dose session. Toward the end of this study, the study team became interested in documenting the occurrence of delayed headache after psilocybin sessions. Of the 11 (of 53) participants queried, two (18%) reported moderate headache following their high dose sessions.

Table 5.3-7: Adverse events reported during dosing sessions

Adverse Event Description*	Low Dose (N = 52)	High Dose (N = 53)
Elevated Diastolic Blood Pressure (> 100)**	1 (2%)	7 (13%)
Elevated Systolic Blood Pressure (> 160)**	9 (17%)	18 (34%)
Elevated Systolic (> 160) and/or Diastolic Blood (> 100)	10 (19%)	18 (34%)
Elevated Heart Rate (> 110)**	1 (2%)	3 (6%)
Mild Headache	0	1 (2%)
Nausea/vomiting	0	8 (15%)
Paranoia	0	1 (2%)
Psychological Discomfort	6 (12%)	17 (32%)
Physical Discomfort	4 (8%)	11(21%)
Anxiety during session	8 (15%)	14 (20%)

* AE during sessions refer to one or more instance(s) of the AE that occurred on session days after capsule administration; in all cases, the AE had resolved by the end of the session day.

** In one participant, the peak blood pressure magnitude (214/114 mmHg) met the protocol criterion for pharmacological treatment, however the protocol criterion for duration of elevation for pharmacological treatment was not met as the event lasted less than 15 minutes. In all cases blood pressure returned to normal levels by the end of the session.

Spontaneously reported adverse events that occurred following psilocybin sessions that were judged to be possibly related to drug administration were rare, with four occurring following the low dose session and one occurring following the high dose session (Table 5.3-8). The reported adverse events judged to be possibly related to drug administration following lower-dose sessions included instances of a feeling of fullness in the chest (n=1), anxiety (n=1), insomnia (n=1) and decreased appetite (n=1). One instance of leg pain occurred following a higher-dose session. There were no cases of hallucinogen persisting perception disorder (HPPD) or prolonged psychosis.

Table 5.3-8: Adverse events reported after the psilocybin dosing session

Adverse Event Description*	Number of Instances	Causality
Death due to disease progression	2	Unrelated
Fullness in chest (post low-dose session)	1	Possible
Anxiety (post low-dose session)	1	Possible
Insomnia (post low-dose session)	1	Possible
Decreased appetite (post low-dose session)	1	Unrelated
Suicide after dropping out of study (did not receive high dose)	1	Unlikely
Eye infection (post low-dose session)	1	Unrelated
Coronary Artery blockage	1	Possible
Leg pain (post high-dose session)	1	Possible
Breast biopsy	1	Unrelated

* AE not during sessions refer to any AE that occurred outside of sessions but after drug exposure during study participation until study termination, dropout, or completion of the six month follow-up; detailed event reports are appended

5.3.4.3.4. Conclusion

When administered in conjunction with psychological support, psilocybin was found to produce substantial and enduring (six-month follow-up) decreases in depressed mood and anxiety in participants with cancer diagnosis versus the comparator (0.014 mg/kg psilocybin) in this setting. The psilocybin treatment was safe and well-tolerated up to 0.31 mg/kg dosing.

5.3.4.4. New York University (NYU) Study

This was a randomized, double-blind, placebo-controlled crossover study (NCT00957359) to investigate the efficacy of a single psilocybin dosing session versus placebo (in conjunction with psychotherapy) to treat clinically significant anxiety or depression in adults who received a cancer diagnosis (Ross et al., 2016). Participants were initially assigned to receive oral psilocybin (0.3mg/kg) or placebo (niacin, 250 mg), administered during an 8-hour treatment session. Crossover to the other arm occurred seven weeks after the first administration. Adverse events were monitored throughout the trial, including during and after dosing sessions. Primary outcomes of potential improvement of participant anxiety and depression were measured through 26 weeks after the second dosing session.

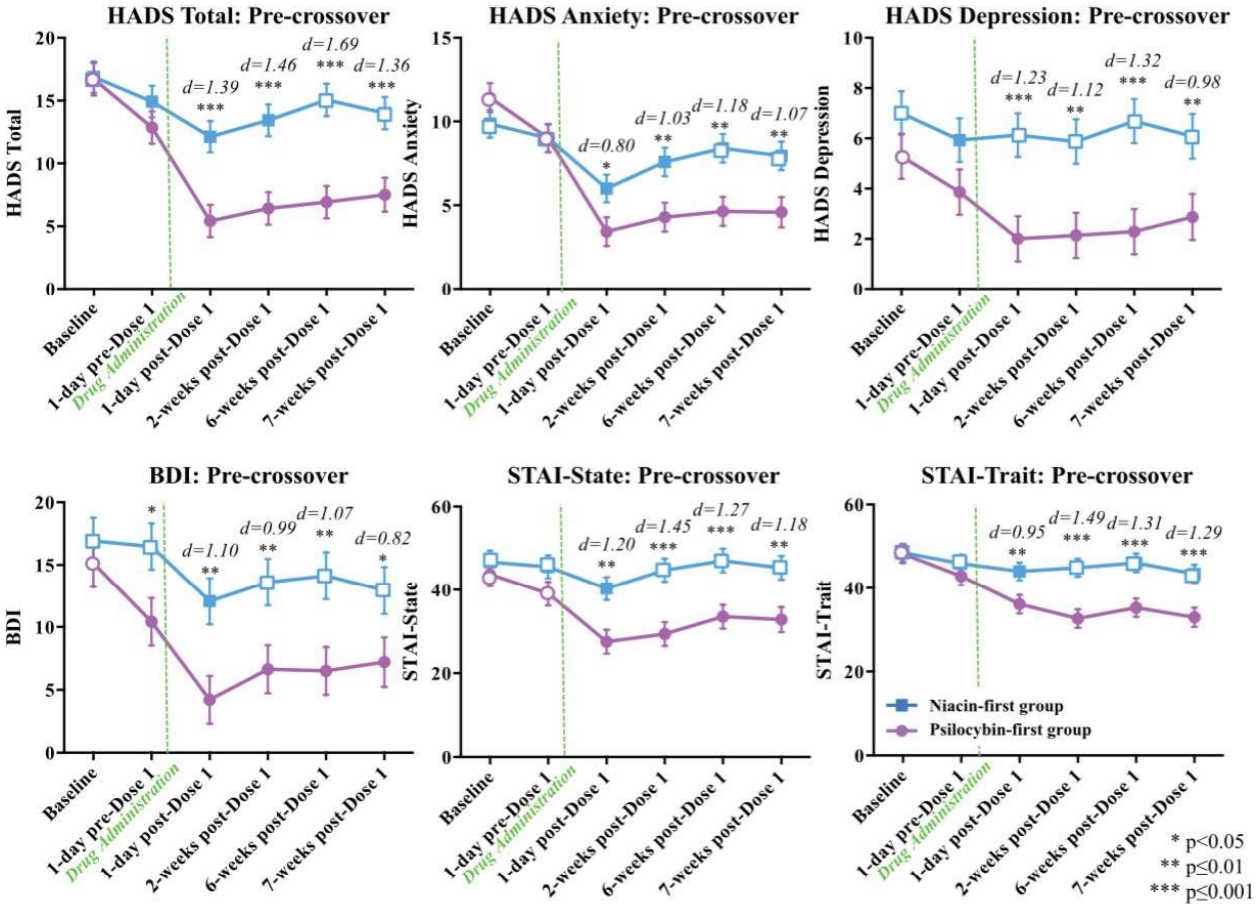
5.3.4.4.1. Results

Thirty-one participants with significant distress due to a cancer diagnosis were initially randomized to receive oral psilocybin (N = 16) or placebo (N = 15). Two participants were removed from the psilocybin arm prior to dosing due to the development of a secondary illness prior to receiving a study intervention. Of the 29 remaining participants who completed the first dosing session, 28 (97%) completed the six-week post-dose follow-up assessments, and 26 (90%) completed the second dose after crossover. Twenty-four participants (83%) completed the second six-week post-dose follow-up, and 23 (79%) completed the six-month follow-up assessments (including one participant who missed the six-week assessment after the second dosing session). Of the 29 participants who completed the first dosing session, four (14%) withdrew due to disease progression, one (3%) passed away, and one (3%) withdrew due to resumption of prohibited concomitant medication.

5.3.4.4.2. Clinical Efficacy

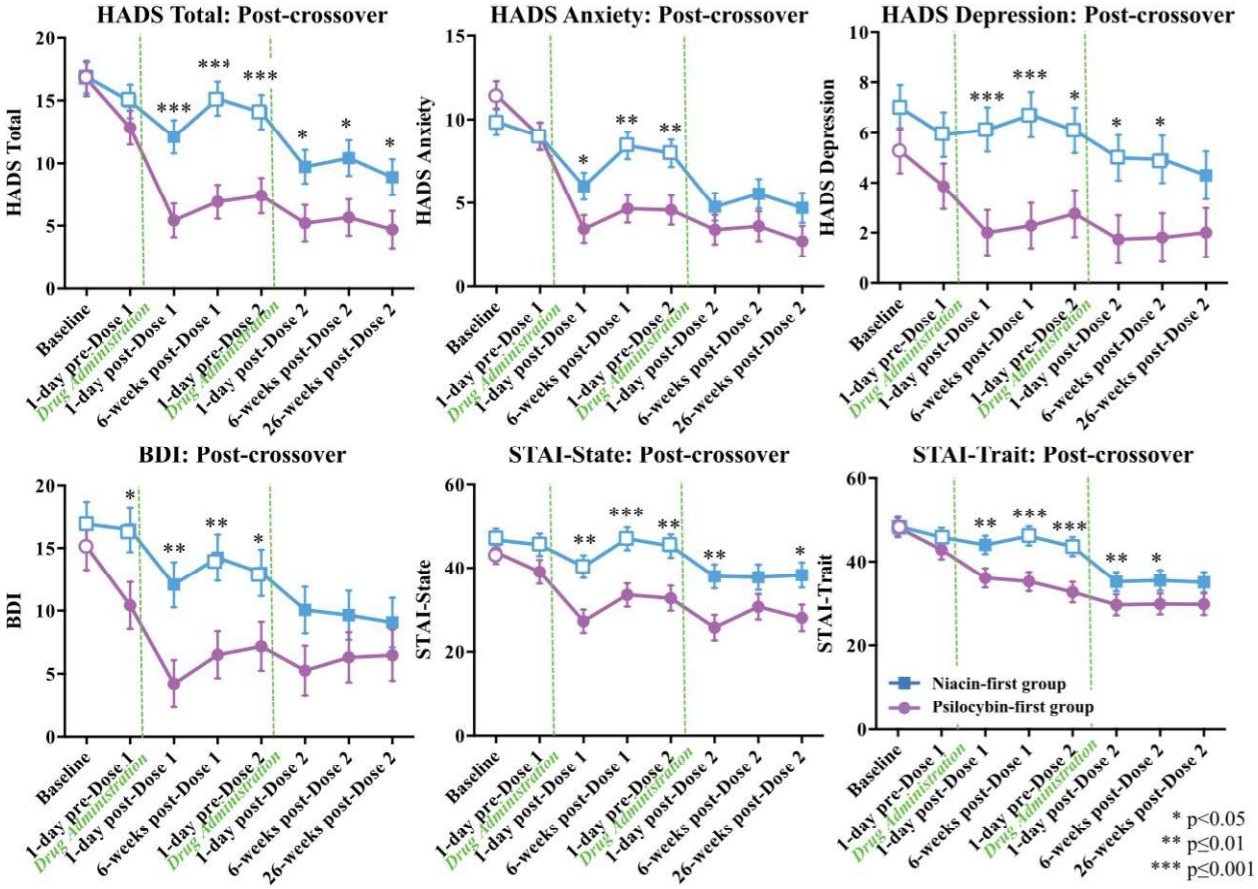
When compared to placebo, a single dose of psilocybin produced a significant acute and sustained reduction in combined anxiety and depressive symptoms as measured by the total Hospital Anxiety and Depression Scale (HADS) score. Compared to baseline and pre-dose results, statistically significant psilocybin efficacy was seen one day following treatment (with persistence through the two-week post-treatment assessment (Figure 5.3-9). Psilocybin showed large effect size advantages for both the depression and anxiety subscales of the HADS based on between-group differences prior to the crossover, as measured by Cohen's d. Convergent support for these effects was provided by similar results on the BDI and trait and state subscales of the STAI (Figure 5.3-9).

Figure 5.3-9: Psilocybin as a method of sustainment for reduction of anxiety and depression in the NYU study. Means (±SE) for primary outcome measures are shown in the two treatment groups at the following time points: baseline (psilocybin first *n*=14, niacin first *n*=15), 1 day pre-dose 1 (psilocybin first *n*=14, niacin first *n*=15), 1 day post-dose 1 (psilocybin first *n*=14, niacin first *n*=15), 2 weeks post-dose 1 (psilocybin first *n*=14, niacin first *n*=14), 6 weeks post-dose 1 (psilocybin first *n*=14, niacin first *n*=14), 7 weeks post-dose 1 (psilocybin first *n*=12, niacin first *n*=14). Asterisks indicate significance level of between-group *t*-tests. Effect sizes, represented as Cohen's d, are shown above time points at which the treatment groups differ. Closed points represent significant within-group differences relative to scores at baseline.



The psilocybin-first group demonstrated significant within-group reductions in all distress measures one day after receiving psilocybin, that endured following the crossover dosing session. Similarly, when the niacin-first group received psilocybin in the crossover, there were significant within-group differences from the day before dosing to the day after and for at least the subsequent 6 months as demonstrated by the following measures: HADS total, HADS anxiety subscale, STAI trait subscale and BDI (Figure 5.3-10). Taken together, these data suggest that the effects of psilocybin persist longer than six weeks post dosing (as represented by the between group comparisons before the crossover) and may be as long as six to nine months in duration from a single dose. In addition to these effects on anxiety and depression, secondary outcomes showed psilocybin significantly impacted related constructs linked to emotional well-being, including quality of life, fear of death, and spiritual well- being.

Figure 5.3-10: Long-term follow-up in the NYU study. Means (±SE) for primary outcome measures are shown in the two treatment groups at the following time points: baseline (psilocybin first *n*=14, niacin first *n*=15), 1-day pre dose-1 (psilocybin first *n*=14, niacin first *n*=15), 1 day post-dose 1 (psilocybin first *n*=14, niacin first *n*=15), 6 weeks post-dose 1 (psilocybin first *n*=14, niacin first *n*=14), 7 weeks post-dose 1 (1 day pre-dose 2) (psilocybin first *n*=12, niacin first *n*=14), 1 day post-dose 2, 6 weeks post-dose 2 (psilocybin first *n*=12, niacin first *n*=11), 26 weeks post-dose 2 (psilocybin first *n*=11, niacin first *n*=12). Asterisks indicate significance level of between-group *t*-tests. Closed points represent significant within-group differences relative to scores at baseline.



5.3.4.4.3. Adverse Events

The most common adverse events that occurred during the psilocybin dosing sessions (before and after crossover, N = 28) included elevated systolic (>160 mm Hg) and diastolic BP (>100 mm Hg), headache and migraine, anxiety, and nausea. None of the elevated BP episodes required pharmacological intervention.

One participant died as a result of cancer disease progression. Four subjects were withdrawn from the study due to disease progression, and passed away shortly after withdrawal from the study. These serious adverse events were not attributed to psilocybin.

Adverse events that occurred outside the dosing sections were collected, and causality from psilocybin was assessed (Table 5.3-9). Three of 11 events (27%) were determined to be possibly

related to psilocybin administration.

Table 5.3-9: Adverse events not occurring during the psilocybin dosing sessions

Adverse Event Description*	Number of Instances	Causality
Community Acquired Pneumonia	1	Unrelated
Death due to disease progression	1	Unrelated
Hypotension	1	Unrelated
Lumbar Spinal Surgery	1	Unrelated
Migraine	1	Unrelated
Ocular Migraine	1	Unrelated
Experience of Thought Disorder	1	Possible
Neurosurgery	1	Unrelated
Visual Field Impairment	1	Possible
Vasovagal Syncopal Event	1	Possible
Vomiting	1	Unrelated

* AE not during sessions refer to any AE that occurred outside of sessions but after drug exposure during study participation until study termination, dropout, or completion of the six month follow-up.

5.3.4.4.4. Conclusion

In this setting, psilocybin was found to produce rapid and sustained effects against anxiety and depression in a population of adults who were diagnosed with cancer. Single-dose psilocybin was well-tolerated at a 0.3 mg/kg dose.

5.3.4.5. Usona Institute PSIL201 Study

Study PSIL201 (NCT03866174) is a randomized, double-blind, active comparator-controlled, support-of-concept Phase 2 study of single-dose psilocybin in subjects with MDD. Eighty participants (males and females) ages 21 to 65 who, at Screening, meet DSM-5 criteria for MDD and meet all other inclusion/exclusion criteria are stratified by study site and randomized with a 1-to-1 allocation under double-blind conditions to receive a single 25 mg oral dose of psilocybin or a single 100 mg oral dose of niacin. Both formulations are visually consistent, excipient-free, and consist of the drug substance encapsulated in an immediate release, hard, white, opaque, size 2, hydroxypropyl methylcellulose capsule. Niacin serves as an active comparator that provides an acute physiological response (flushing) that is intended to aid in blinding of intervention allocation. Participants deemed eligible following successful completion of all screening assessments complete central rater, on-site rater and self-report measures at Baseline for a final eligibility determination. Eligible participants at Baseline undergo preparation sessions and are eligible for randomization on Dosing Day to receive either psilocybin or niacin active-comparator; they complete follow-up visits and assessments on study Day 2, 8, 15, 29 and 43 (within corresponding visit windows). Study outcome measures assess depressive symptoms, clinical global functioning, functional disability, anxiety symptoms and health-related quality of life. Safety outcome measures are collected at all assessment time points from the time of consent through the end of study.

To enhance participant safety, Study PSIL201 utilizes a "set and setting" (SaS) approach similar to the protocol that has been used in modern studies of psilocybin in both diseased and normal healthy populations. The SaS protocol for this study includes: 1) a period of preparation with session Facilitators prior to dosing; 2) administration of study medications in an aesthetically pleasing room under the supervision of two Facilitators who are present throughout the session (with the exception of short, temporary allowances for facilitator breaks; e.g. bathroom breaks); and 3) three post-dose integration sessions during which participants are encouraged to discuss their intervention experience with the Facilitators.

Participant enrollment for Study PSIL201 began in January 2020. As of the drafting of the current version of this Investigator Brochure, five participants have enrolled and five participants have completed study PSIL201. Of the five participants who have completed study PSIL201, no unexpected TEAEs and no SAEs have occurred.

Table 5.3-10: Usona Institute PSIL201 study overview

Planned Enrollment	Design	Duration of Treatment/ Dosing Regimen	Study Population	FSFV[1]	Subject Exposure per Treatment Arm (M/F)
n=80	Randomized, double-blind, active placebo-controlled safety and efficacy study	Single dose	Adults (age 21-65) with MDD	19DEC2019	Planned: 40:40 (~20M and ~20F per arm)

F: Female; FSFV: First subject first visit; M: Male; MDD: Major Depressive Disorder

[1] FSFV date is considered the first date on which a subject signed the informed consent form

5.3.4.6. Usona Institute PSIL201 Long-Term Follow-Up Study (PSIL201-LTFU)

Study PSIL201-LTFU is a double-blind, long-term observational follow-up study of all randomized subjects in Study PSIL201. Participants providing informed consent will be enrolled into the study and will complete web surveys and telephone interviews conducted by one central site at the following time intervals: Months 2, 3, 4, 5 and 6 (± 7 days for each assessment) and Months 8, 10, 12, 14, 16, 18, 20, 22 and 24 (± 14 days for each assessment) [all visit dates in this study are relative to the date of dosing in Study PSIL201]. Site personnel and participants will remain blinded to any information that might directly reveal the treatment assignment from Study PSIL201. Observational assessments will include self-reported outcomes conducted via web or paper survey and the following measures conducted by the central site via telephone: 1) a record of concomitant medication/therapy use, 2) the Montgomery-Åsberg Depression Rating Scale [MADRS], 3) a review of DSM-5 diagnostic criteria for Major Depressive Disorder, 4) the Sheehan Disability Scale [SDS], 5) a review of solicited adverse events, and 6) the Columbia-Suicide Severity Rating Scale [C-SSRS].

5.3.5. Summary of the Clinical Safety of Psilocybin in Clinical Trials

Over the course of its clinical development phase, thousands of participants have received psilocybin under controlled conditions in a clinical setting for various indications, with subsequent

results published in peer-reviewed journals (J. Rucker, Iliff, & Nutt, 2017; Metzner, 2005). As these studies were predominantly performed in an academic setting, safety reporting criteria and the level of data verification varied greatly between studies, but these data can be utilized to elucidate the expected adverse event profile of psilocybin.

Overall, the most commonly reported adverse events associated with psilocybin administration are psychological in nature and include anxiety, the induction of negative emotional states and paranoid/delusional thinking during psilocybin sessions, as well as far less frequent reports of Hallucinogen Persisting Perception Disorder (HPPD) (M. Johnson, Richards, & Griffiths, 2008; Tylš et al., 2014). Rates of prolonged psychiatric symptoms of any kind following psilocybin exposure in healthy study participants are estimated to be 0.08-0.09%. Cardiovascular changes including increased BP and heart rate, nausea, and headaches are also commonly reported with psilocybin administration. These events are therefore examined further in this section.

5.3.5.1. Hallucinogen Persisting Perception Disorder (HPPD)

Some people who have used serotonergic hallucinogens, such as psilocybin, experience persistent, distressing alterations in mostly visual perception that last from weeks to years after use (Espiard, Lecardeur, Abadie, Halbecq, & Dollfus, 2005). This condition is now diagnosed as hallucinogen persistent perception disorder (HPPD). To date, however, no cases of HPPD have occurred in volunteers given psilocybin in current research studies (Studerus et al., 2011). In studies involving cancer patients examining cancer related anxiety and depression, no cases of HPPD were identified and no participants developed any symptoms of paranoia or anxiety that required pharmacological intervention or anything more than reassurance from session facilitators. The risk of HPPD occurring after psilocybin administration can be reduced by screening participants for potential risk factors such as substance dependence and by excluding people reporting HPPD or other significant adverse events after prior use of hallucinogens.

5.3.5.2. Cardiovascular

5.3.5.2.1. QTc

In the **University of Wisconsin Study** (Phase 1 dose escalation of oral psilocybin in healthy participants), additional analysis was performed in order to ascertain the effect of psilocin concentration on QTc interval prolongation. Blood samples for PK assessment were collected at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hours post dose. 12-lead ECG were obtained predose, 2, 4 and 8 hours post-dose. The ECGs, including QTcB and QTcF durations, were overread by an electrophysiologist. The study did not include a placebo arm or a positive control arm.

The studied psilocybin doses ranged from 19 to 59 mg (0.3 to 0.6 mg/kg) and psilocin C_{max} ranged from 11 to 54 ng/mL. No delay between the time course of psilocin PK and the change in ΔQTcF was observed, with maximum ΔQTcF occurring at the time of psilocin C_{max}. The concentration-QTc analysis showed a positive effect of psilocybin on QTcF prolongation with a linear relationship between psilocin Cmax and ΔQTcF, under the studied psilocybin doses. The upper bound of the 90%CI of the model-predicted mean ΔQTcF crosses the threshold of regulatory concern of 10 msec at a psilocin concentration of 31.1 ng/mL. At the therapeutic dose of 25 mg, the expected mean

psilocin C_{max} is about 18.7 ng/mL and the associated upper bound of the 90%CI of the predicted mean ΔQTcF is 6.6 msec, below the threshold of 10 msec. The values for the median C_{max}, model-predicted mean ΔQTcF, and upper and lower 90% confidence interval (CI) limits for the change in QTcF at any of the ECG samplings are shown below (Table 5.3-11).

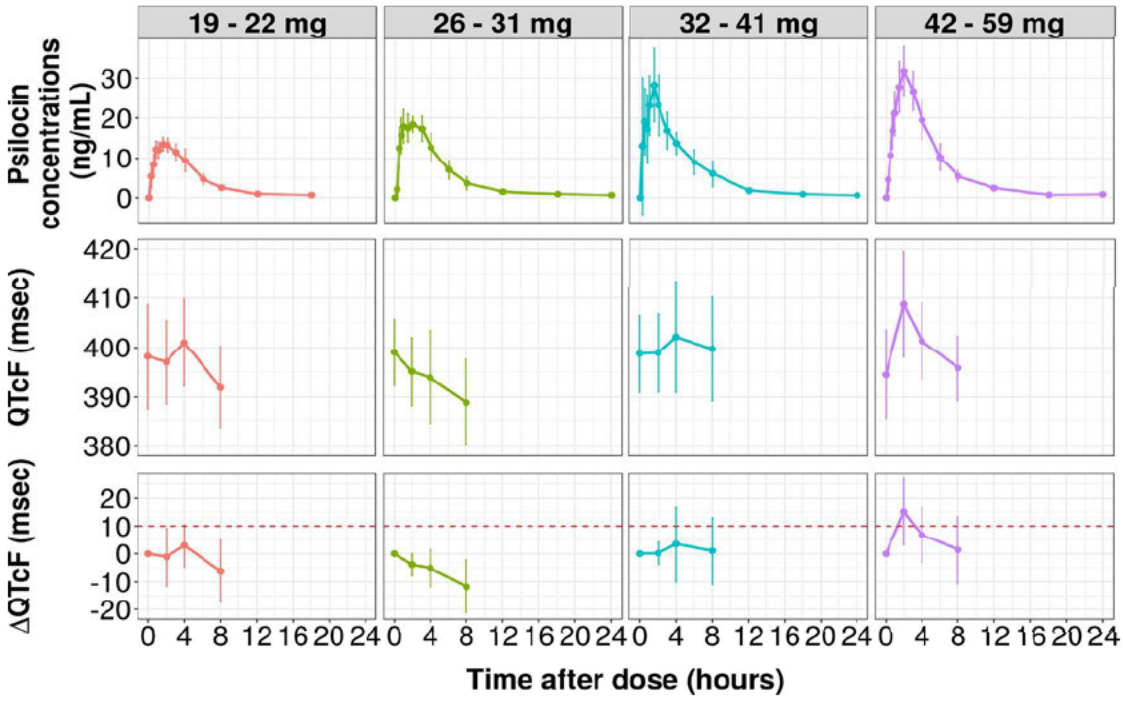
Data is unpublished; information was obtained from final draft of QTc specific technical report generated by Joga Gobburu, PhD and his team at University of Maryland.

Table 5.3-11: Model-predicted mean ΔQTcF at the observed median Cmax of each dose quartile

Dose / Dose range	Median Cmax (ng/mL)	Model-predicted mean ΔQTcF (msec)	Lower 90% CI of mean ΔQTcF (msec)	Upper 90% CI of mean ΔQTcF (msec)
19 - 22 mg	15.3	1.5	-2.7	5.7
25 mg	18.7	2.1	-2.4	6.6
26 - 31 mg	24.3	3.0	-2.1	8.1
32 - 41 mg	29.8	3.9	-1.7	9.6
42 - 59 mg	37.6	5.3	-1.2	11.8

The psilocin concentrations as compared with QTcF are shown over time for dose group in Figure 5.3-11.

Figure 5.3-11: Time course of mean (± 90%CI) psilocin concentrations, QTcF and baseline-adjusted QTcF. (ΔQTcF) intervals in each psilocybin dose quartile.



5.3.5.2.2. Blood Pressure

Higher doses of psilocybin (>0.3 mg/kg) also may transiently lead to elevated mean blood pressure, peaking 30-60 min following psilocybin administration and returning to baseline levels after 90-180 min without necessitating further interventions.(Griffiths et al., 2006; Hasler, Grimberg, Benz, Huber, & Vollenweider, 2004) The severity of elevations in blood pressure were usually asymptomatic, and were graded as mild or moderate (CTCAE Grade 1 or 2, respectively). Although several subjects in the University of Wisconsin dose escalation study reached blood pressure elevations that were graded as moderate, they remained asymptomatic. It is not clear whether the changes in blood pressure and heart rate are due to the elevated psilocin concentration directly or to the psychedelic effect caused by this active metabolite. Psilocybin appears to produce only slight sympathetic system activation. Psilocybin may elevate prolactin, but not cortisol or ACTH (Gouzoulis-Mayfrank, Thelen, et al., 1999) with prolactin elevation no longer detectable 300 minutes post-drug (Hasler et al., 2004).

5.3.5.2.3. Heart Rate

Transient elevations of heart rate are common in subjects receiving doses of psilocybin at doses of 0.3 mg/kg or more. The time course of these elevations in heart rate are similar to those seen for the elevations in blood pressure, peaking between 60-120 minutes after the dose. This is similar to the time of peak psilocin concentrations and peak psychedelic effect. Again, it is not clear whether the changes in blood pressure and heart rate are directly due to the elevated psilocin concentration or caused indirectly by the psychedelic effect. In the Wisconsin Phase I dose-escalation study, there were several instances in which mild bradycardia was noted. Instances of bradycardia or tachycardia were unimodal, with no swing between bradycardia and tachycardia after a given dose. The episodes of bradycardia and tachycardia reported in current studies at NYU, Johns Hopkins, and Wisconsin were asymptomatic ("mild" or CTCAE Grade 1) and did not require treatment.

5.3.5.2.4. Headache

Mild headaches are common within the 24 hours after a dose of psilocybin. No auras or photo/phonophobia are associated with these headaches, which respond well to a single dose of acetaminophen. The headaches did not appear to be dose-related in the University of Wisconsin study, with no higher incidence after doses of 0.6 mg/kg vs 0.3 mg/kg.

6. SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

6.1. Summary of Data

Psilocybin is a tryptamine derivative that can be enzymatically cleaved in the body to produce psilocin, an agonist at a variety of serotonin receptors. The pharmacokinetics, pharmacology and human metabolism of psilocybin are well known and well characterized. In conjunction with psychotherapy, psilocybin has been utilized broadly in Phase 2 clinical trials conducted in the academic setting, including in improving symptoms of anxiety, depression, and substance use disorder.

The clinical safety of psilocybin has been extensively studied, both as a single agent and as adjunctive treatment in adult populations. Psilocybin is administered orally, and has been studied in open-label, and double-blind, controlled trials. Dosing regimens have ranged from 0.014 mg/kg to 0.6 mg/kg, administered as either a single dose, or multiple doses weeks apart.

The most common adverse experiences are psychological, including anxiety, and the induction of negative emotional states and paranoid/delusional thinking during psilocybin sessions. The most common physical adverse events are cardiovascular (increased blood pressure and heart rate), as well as nausea and headache.

Psilocybin capsules should be stored in a secure location at room temperature.

6.2. Method of Administration

A capsule of psilocybin is administered orally with a full glass of water, as per the study protocol. As described under Special Warnings and Special Precautions for Use, the study drug must be administered to participants who have been screened for psychiatric and other risk factors for an adverse psychedelic experience, per protocol. The participant must have adequate counselling and preparation ahead of dosing, and after ingesting the dose must be attended by at least one Facilitator, but preferably two, for the subsequent 6-8 hours.

6.3. Dose Response

A meta-analysis of eight double-blind placebo-controlled studies including 110 healthy subjects who had received 1–4 oral doses of psilocybin (45–315 µg /kg body weight) showed that effects of psilocybin are dose-dependent, although other factors such as personality structure and the setting (e.g. environment) appear to modulate its overall effects (Preller et al., 2016; Studerus, Gamma, Kometer, & Vollenweider, 2012). Although psilocybin dose-dependently induced profound changes in mood, perception, thought, and self-experience, most subjects described the experience as pleasurable, enriching, and non-threatening. Acute adverse drug reactions, characterized by strong dysphoria and/or anxiety/panic, occurred transiently only in the two highest dose conditions in a relatively small proportion of subjects (5 and 8% respectively). All acute adverse drug reactions were successfully managed by providing interpersonal support and did not require psychopharmacological intervention. In fact, individual reactions to serotonergic

hallucinogens can vary, even when the experimental conditions are consistently maintained (Dittrich, 1994; Nichols & Chemel, 2006).

A meta-analysis of psilocybin effects (dose range from 0.115–0.315 mg/kg) in a sample of 261 healthy volunteers found that drug dose, the personality trait absorption, a positron emission tomography (PET) scanning environment, and age were significant factors predicting response to psilocybin (Studerus et al., 2012). Specifically, higher dose predicted greater overall drug effects. Greater personality absorption predicted higher "oceanic boundlessness" scores on the five dimensional Altered State of Consciousness (ASC) — a scale that measures the positively experienced loss of self/ego boundaries associated with heightened mood, bliss and derealisation phenomena. Lower age and conducting the study in the PET scanner environment predicted greater anxiety (Studerus et al., 2012). Participant gender was not found to have any significant effects on psilocybin response,(Studerus et al., 2012) consistent with the limited human data examining sex differences in classic psychedelics' effects (Leary, Litwin, & Metzner, 1963).

6.3.1. Dose Modification

Dose modification is not applicable. Psilocybin is administered as a single, fixed dose.

6.4. Contraindications

Psilocybin is contraindicated in participants who are on monoamine oxidase inhibitors or who have a known sensitivity to the drug or its metabolites. It is contraindicated in medications that are known uridine diphosphate glucuronosyltransferase enzyme modulators. It is contraindicated in patients with schizophrenia or bipolar disease, or in those with first degree relatives with these disorders. The concurrent use of selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitors (SSRI/SNRI) medications is assumed to be contraindicated due to the potential to increase the risk of serotonin syndrome and/or to attenuate the binding of psilocin to the HT2A receptor.

6.5. Special Warnings and Special Precautions for Use

Prior to enrollment participants must first be screened per the clinical protocol for contraindicated psychologic conditions or interacting medications. Appropriate counselling and preparation for the session typically requires approximately 6-8 hours (M. Johnson et al., 2008).

Dosing with psilocybin must be also performed per the clinical protocol. This is typically in a setting that minimizes distraction and interruption, and the patient is attended following the dose by a therapist trained in providing reassurance and a safe environment until the effects of the single dose have dissipated. Upon discharge from the study setting, the patient should be delivered to the care of a responsible individual who can observe the patient for the remainder of 24 hours after the dose was administered.

Although there have been no reports of their use in well reported clinical trials with oral psilocybin, medications should be available for the treatment of causal symptomatic hypertension, agitation, or severe psychosis. Typically, these supplies are two dosage units of labetalol, nitroglycerin, lorazepam and/or diazepam, and risperidone or similar orally-disintegrating antipsychotic.

6.5.1. Undesirable Effects

6.5.1.1. Physical Adverse Effects

Previous studies in healthy participants have shown oral psilocybin to be well-tolerated. No drug-related serious adverse events were reported.

The Phase 1 **University of Wisconsin Study**, a completed, open-label, dose-escalating (0.3 - 0.6 mg/kg oral psilocybin) trial described safety events in 12 healthy participants. 10 of 12 participants (83%) reported mild hypertension, 9 of 12 (75%) reported mild headache, 7 of 12 (58%) reported mild bradycardia, and 6 of 12 (50%) reported mild tachycardia. Other mild events affecting fewer than 50% of the study participants included hypotension, fever, fatigue, nausea, diarrhea, and dizziness. Four of 12 (33%) of participants reported moderate hypertension. Dose strength was not found to correlate to adverse event frequency.

The retrospective **University of Zurich** study described subjective, participant-reported events in a population of 110 healthy volunteers across eight clinical trials. The most frequent self-reported adverse experiences reported were mild headache (M. W. Johnson, Sewell, & Griffiths, 2012), and mild lethargy (fatigue, exhaustion, or lack of energy) immediately after psilocybin administration. For these events, normal function was largely restored after 24 hours. Three participants were withdrawn from their respective studies due to adverse events caused by psilocybin (two had unusually intense reaction to low-dose psilocybin, and one experienced a transient hypotonic reaction with dizziness, fainting and vomiting after receiving low-dose psilocybin). In each case, symptoms were completely resolved by the end of the dosing day.

Additional studies detailed the most common physical adverse events as cardiovascular (increased BP and heart rate), as well as nausea and headache.

6.5.1.2. Behavioral and Psychologic Adverse Effects

The most likely potential acute adverse effects of psilocybin were shown to be anxiety, as well as panic, delusion, and cognitive impairments, particularly at higher doses (> 25 mg oral psilocybin) during the period of acute drug action. Such transient episodes of fear or anxiety respond well to reassurance and have not required pharmacological intervention. In previous clinical experience, acute psychological events were resolved by the end of the dosing day.

Rates of prolonged psychiatric symptoms of any kind following psilocybin exposure in healthy study participants are estimated to be 0.08-0.09%. These include the possibility of prolonged adverse psychological reactions, such as psychosis and depression.

The low rate of enduring psychological symptoms is consistent with a summary of such effects from the **University of Zurich** study. In that retrospective analysis, seven participants endorsed negative changes in psychological well-being, but only one participant (0.9%) reported a level of distress sufficient for him to contact the researchers. Those symptoms were resolved after a few sessions with an experienced psychotherapist.

6.5.2. Interactions

After administration psilocybin is rapidly metabolized (via dephosphorylation) to psilocin, the active molecule. This is further glucuronidated by the uridine diphosphate glucuronosyltransferase UGT1A9 and 1A10, and deaminated to 4-hydroxyindoles by monoamine oxidase, and aldehyde and alcohol dehydrogenase. The pharmacologic activity of the metabolites of psilocin are not known and no controlled studies of the effect of other drugs upon psilocybin metabolism / pharmacokinetics or effect have been performed. Inhibitors of UGT1A9 and 1A10 would be expected to increase the C_{max} and Area Under the Curve (AUC) of psilocin, and should be discontinued at least five half-lives prior to the administration of psilocybin. Similarly, monoamine oxidase and aldehyde or alcohol dehydrogenase inhibitors should be discontinued at least 5 half-lives prior to the dose of psilocybin.

6.5.3. Use During Pregnancy and Lactation

There have been no human case reports or studies involving the effects of psilocybin on pregnancy. It is recommended that women who are pregnant avoid using psilocybin. Women of childbearing potential who have a negative pregnancy test at screening will undergo repeated pregnancy testing prior to treatment administration, and only if the results are negative the morning of treatment will psilocybin or placebo be administered. Any pregnancy occurring after study enrollment should be followed until an outcome is known. (i.e., spontaneous miscarriage, elective termination, normal birth). All live births must be followed for a minimum of 30 days or to the first well-baby visit.

Non-clinical and clinical data describing the effects of oral psilocybin on lactation, sperm, and teratogenicity are not available.

6.5.4. Carcinogenesis and Mutagenesis

Non-clinical and clinical data describing carcinogenic and metagenetic effects of oral psilocybin are not available.

6.5.5. Overdose

There are no confirmed reports of an overdose of pharmaceutical psilocybin. Previous clinical trials involved single or multiple doses of oral psilocybin in predefined quantities, administered in a controlled environment. Oral psilocybin, 25 mg capsules, are within the dosing range previously shown to be safe and well-tolerated. Should an accidental overdose occur, appropriate symptomatic measures should be initiated, followed by monitoring any adverse events to resolution.

6.5.6. Abuse Potential

Currently, psilocybin is placed in Schedule 1, defined as having no medical use, possessing high abuse liability, and no safety when used under medical supervision. However, in preclinical studies, psilocybin, mescaline and NN-DMT did not serve as positive reinforcers in MDMA-experienced rhesus monkeys argues strongly that monkeys at least do not find the psychoactive effects of the 5- HT2A receptor agonists rewarding (Heal, Gosden, & Smith, 2018).

In previous clinical studies with psilocybin, exposing individuals with either no history of hallucinogen use or a history of minimal use (e.g. less than 10 times total and not within the last five years) in the context of a supervised and controlled research setting has not resulted in reported instances of subsequent illicit hallucinogen abuse (Griffiths et al., 2011; Griffiths et al., 2006). Additionally, these recent studies have shown side effects including acute elevations in fear and anxiety, aspects that are potentially predictive of low abuse potential (M. W. Johnson, Griffiths, Hendricks, & Henningfield, 2018). Based on available literature, it is not expected that either psilocybin-naïve or experienced individuals will develop dependence after exposure.

Additional survey research within the Unites States suggests hallucinogens were selected as a primary substance of abuse in only a fraction of a percentage of responders (M. W. Johnson et al., 2018). Continuing, in the University of Zurich study the large majority of participants reported "no change" in their psilocybin use following their laboratory sessions, as well as "no change" in their overall drug consumption habits (e.g., use of alcohol, nicotine, cannabis, MDMA). Those who did report changes often described decreased consumption, specifically in terms of psilocybin use.

6.5.7. Ability to Drive and Use Machines

Participants must agree to be driven home following dosing with psilocybin. The clinical protocol must be followed regarding patient discharge after dosing.

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V–53 [Amended]

From Charleston, SC; Columbia, SC; Spartanburg, SC; Sugarloaf Mountain, NC; to Holston Mountain, TN. From Lexington, KY; Louisville, KY; INT Louisville 333° and Brickyard, IN, 170° radials; Brickyard. The airspace within R–3401B is excluded.

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V–115 [Amended]

From Crestview, FL; INT Crestview 001° and Montgomery, AL, 204° radials; Montgomery; INT Montgomery 323° and Vulcan, AL, 177° radials; Vulcan; Choo Choo, TN; to Volunteer, TN. From Charleston, WV; to Parkersburg, WV.

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V–140 [Amended]

From Panhandle, TX; Burns Flat, OK; Kingfisher, OK; INT Kingfisher 072° and Tulsa, OK, 261° radials; Tulsa; Razorback, AR; Harrison, AR; Walnut Ridge, AR; Dyersburg, TN; Nashville, TN; Livingston, TN; to London, KY. From Bluefield, WV; INT Bluefield 071° and Montebello, VA, 250° radials; Montebello; to Casanova, VA.

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V–339 [Removed]

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6011 United States Area Navigation Routes.

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T–215 Holston Mountain, TN (HMV) to Gamke, IN [Amended]

Holston Mountain, TN (HMV)	VORTAC	(Lat. 36°26′13.40″ N, long. 082°07′46.56″ W)
HILTO, VA	WP	(Lat. 36°41′48.46″ N, long. 082°26′07.44″ W)
FLENR, VA	WP	(Lat. 36°56′44.27″ N, long. 082°43′42.75″ W)
RISTE, KY	WP	(Lat. 37°09′02.92″ N, long. 082°58′24.38″ W)
Hazard, KY (AZQ)	DME	(Lat. 37°23′28.52″ N, long. 083°15′46.83″ W)
HUGEN, KY	FIX	(Lat. 37°31′46.14″ N, long. 083°32′58.54″ W)
Lexington, KY (HYK)	VOR/DME	(Lat. 37°57′58.86″ N, long. 084°28′21.06″ W)
GAMKE, IN	WP	(Lat. 38°46′12.99″ N, long. 085°14′35.37″ W)

* * * * * * *

T–323 CROCS, GA to Hazard, KY (AZQ) [Amended]

CROCS, GA	WP	(Lat. 32°27′17.69″ N, long. 082°46′29.06″ W)
BOBBR, GA	WP	(Lat. 33°19′57.07″ N, long. 083°08′19.47″ W)
BIGNN, GA	WP	(Lat. 34°20′34.38″ N, long. 083°33′06.80″ W)
ZPPLN, NC	WP	(Lat. 34°59′47.42″ N, long. 083°49′37.73″ W)
HIGGI, NC	WP	(Lat. 35°26′46.57″ N, long. 083°46′41.05″ W)
KIDBE, TN	WP	(Lat. 35°51′16.23″ N, long. 083°40′19.66″ W)
ZADOT, TN	WP	(Lat. 36°35′32.17″ N, long. 083°28′40.09″ W)
WELLA, KY	WP	(Lat. 37°02′15.68″ N, long. 083°21′31.07″ W)
Hazard, KY (AZQ)	DME	(Lat. 37°23′28.52″ N, long. 083°15′46.83″ W)

* * * * *

Issued in Washington, DC, on July 20, 2020.

Scott M. Rosenbloom,

Acting Manager, Rules and Regulations Group.

[FR Doc. 2020–15992 Filed 7–23–20; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 300

[Docket No. FDA–2019–N–5553]

RIN 0910–AI36

Annual Summary Reporting Requirements Under the Right to Try Act

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: To facilitate implementation of the reporting requirements of the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017 (Right to Try Act), the Food and Drug Administration (FDA, the Agency, or we) is proposing to establish requirements for the deadline and contents of submission of an annual summary. This proposed rule, if finalized, would implement the statutory requirement under provisions of the Right to Try Act for submission of an annual summary by sponsors and manufacturers who provide an eligible investigational drug for use by an eligible patient.

DATES: Submit either electronic or written comments on the proposed rule by September 22, 2020. Submit comments on information collection issues under the Paperwork Reduction Act of 1995 by September 22, 2020.

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before September 22, 2020. The *https://www.regulations.gov* electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of September 22, 2020]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- *Federal eRulemaking Portal: https://www.regulations.gov.* Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to *https://www.regulations.gov* will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on *https://www.regulations.gov.*
- If you want to submit a comment with confidential information that you do not wish to be made available to the public submit the comment as a written/paper submission and in the manner detailed (see ''Written/Paper Submissions'' and ''Instructions.'')

Written/Paper Submissions

Submit written/paper submissions as follows:

- *Mail/Hand Delivery/Courier (for written/paper submissions):* Dockets Management Staff (HFA–305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for

information submitted, marked and identified, as confidential, if submitted as detailed in ''Instructions.''

Instructions: All submissions received must include the Docket No. FDA–2019–N–5553 for ''Annual Summary Reporting Requirements Under the Right to Try Act.'' Received comments, those filed in a timely manner (see **ADDRESSES**), will be placed in the docket and, except for those submitted as ''Confidential Submissions,'' publicly viewable at *https://www.regulations.gov* or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240–402–7500.

- Confidential Submissions—To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states ''THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.'' The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on *https://www.regulations.gov*. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as ''confidential.'' Any information marked as ''confidential'' will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: *https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf*.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to *https://www.regulations.gov* and insert the docket number, found in brackets in the heading of this document, into the ''Search'' box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240–402–7500.

Submit comments on the information collection issues under the Paperwork Reduction Act of 1995 to the Office of Management and Budget (OMB) at *https://www.reginfo.gov/public/do/PRAMain.* Find this particular information collection by selecting ''Currently under Review—Open for Public Comments'' or by using the search function. The title of this proposed collection is ''Annual Summary Reporting Requirements Under the Right to Try Act.''

FOR FURTHER INFORMATION CONTACT: Kathleen Davies, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 32, Rm. 3121, Silver Spring, MD 20993, 301–796–2205, *kathleen.davies@fda.hhs.gov.*

With regard to the information collection: Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North 10A–12M, 11601 Landsdown St., North Bethesda, MD 20852, 301–796–5733, *PRAStaff@fda.hhs.gov.*

SUPPLEMENTARY INFORMATION:

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I. Executive Summary

A. Purpose of the Proposed Rule

The purpose of this proposed rule is to implement section 561B(d)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360bbb–0a(d)(1)), added by the Right to Try Act, which requires sponsors and manufacturers who provide an ''eligible investigational drug'' under section 561B of the FD&C Act to submit to FDA an annual summary of such use, and directs FDA to specify by regulation the deadline of submission. The proposed rule, if finalized, would provide information on the necessary contents of the annual summary and the deadline for its submission.

B. Summary of the Major Provisions of the Proposed Rule

The proposed rule would add § 300.200 to part 300 (21 CFR part 300) as a new subpart D, to specify the deadline and content for submission of an annual summary of investigational drugs supplied under section 561B of the FD&C Act, and the uses for which they were supplied. The manufacturer or sponsor of an eligible investigational drug shall submit to FDA an annual summary of any use of such drug supplied under section 561B of the FD&C Act. Per the statute, the summary shall include the number of doses supplied, the number of patients treated, the use for which the drug was made available, and any known serious adverse events from use of the drug.

C. Legal Authority

Section 561B of the FD&C Act, in conjunction with FDA's general rulemaking authority in section 701(a) of the FD&C Act (21 U.S.C. 371(a)), serve as FDA's legal authority for this proposed rule.

D. Costs and Benefits

This proposed rule, if finalized, would establish the deadline for submission of annual summaries of use of investigational drugs supplied under the Right to Try Act. The proposed rule would also establish the required contents of these submissions. Costs are estimated as the time spent by firms to prepare and submit these annual summary reports. The total estimated present value of this rule's costs is $39,991991 at a seven percent discount rate and $49,345345 at a three percent discount rate (in 2018 dollars). The annualized cost of this rule over 10 years is $5,694694 at a seven percent discount rate and $5,785785 at a three percent discount rate.

We are unable to quantify the expected benefits of this proposed rule because there is no data that would allow us to predict the extent to which direct benefits would be generated. The benefits of this rule consist of societal and public health outcomes that may accrue from the disclosure of the use of investigational drugs and any known serious adverse events provided in these annual summary reports. Without these reports, FDA would not be made aware in a systematic manner of the use of eligible drugs under the Right to Try Act and any known serious adverse events. With these reports, there may be increased awareness of investigational drugs, the diseases or conditions for which patients are seeking access, and

any known serious adverse events associated with such use.

These reporting requirements instruct firms to collect all known serious adverse events and submit them once per year to FDA. In addition, based on the information in these annual summaries, FDA intends to post online an annual summary report in accordance with section 561B(d)(2) of the FD&C Act. FDA's posting of these reports may increase awareness about the availability of investigational drugs.

II. Background

A. Introduction

On May 30, 2018, the Right to Try Act (Pub. L. 115–176) was signed into law, creating section 561B of the FD&C Act. The Right to Try Act amends the FD&C Act to establish an option for patients who meet certain criteria to request access to certain unapproved medical products, and for sponsors and manufacturers who agree to provide certain unapproved medical products other than through FDA's expanded access program.[1] This law provides a new pathway for patients to request, and manufacturers or sponsors to choose to provide, access to certain unapproved, investigational drugs, including biological products, for patients diagnosed with life-threatening diseases or conditions (as defined in § 312.81 (21 CFR 312.81)) who, as certified by a physician, have exhausted approved treatment options and who are unable to participate in a clinical trial involving the investigational drug.[2] This proposed rule is not proposing to require that physician determinations be submitted to FDA. Manufacturers or sponsors who provide their investigational product under the Right to Try Act are required to submit to FDA an annual summary of the use of their drug. Specifically, manufacturers or sponsors of an eligible investigational drug must submit to FDA an annual summary that includes the number of doses supplied of an eligible investigational drug, the number of patients treated, the use for which the drug was made available, and any known serious adverse events. Per section 561B of the FD&C Act, FDA is required to specify, through regulation, the deadline for such submissions (section 561B(d)(1)). This proposed rule, if finalized, would specify that deadline.

B. Criteria for Use Under Section 561B of the FD&C Act

The Right to Try Act provides a pathway for patients who meet certain criteria (*i.e.,* eligible patients) to request, and manufacturers or sponsors to choose to provide access, to eligible investigational drugs under certain conditions. An eligible patient, as defined in the Right to Try Act, is a patient who has:

- Been diagnosed with a life-threatening disease or condition, as defined in § 312.81 (or any successor regulations) (section 561B(a)(1)(A));
- Exhausted approved treatment options and is unable to participate in a clinical trial involving the eligible investigational drug (this must be certified by a physician who is in good standing with their licensing organization or board and who will not be compensated directly by the manufacturer for so certifying) (section 561B(a)(1)(B)); and
- Provided, or their legally authorized representative has provided, to the treating physician written informed consent regarding the eligible investigational drug (section 561B(a)(1)(C)).

An eligible investigational drug, as defined in the Right to Try Act, is an investigational drug, including a biological product:

- For which a Phase 1 clinical trial (as described in 21 CFR 312.21) has been completed (section 561B(a)(2)(A));
- That has not been approved or licensed for any use by FDA (section 561B(a)(2)(B));
- For which an application has been filed with FDA, or that is under investigation in a clinical trial that is intended to form the primary basis of a claim of effectiveness in support of FDA approval or licensure and is the subject of an active investigational new drug application submitted to FDA (section 561B(a)(2)(C)); and
- Whose active development or production is ongoing, and that has not been discontinued by the manufacturer or placed on clinical hold by FDA (section 561B(a)(2)(D)).

A manufacturer or sponsor is in the best position under the Right to Try Act to determine if an investigational drug meets these criteria. In contrast, if patients contact FDA with questions about whether a product is eligible, FDA likely will not be able to answer such inquiries because disclosure laws and regulations generally prevent the Agency from publicly sharing information about the status or existence of an investigational new drug application (IND). For these reasons, under this proposed rule, FDA is not proposing to make determinations about whether a particular investigational product is an eligible investigational drug under the Right to Try Act.

III. Legal Authority

The Right to Try Act amended Chapter V of the FD&C Act by inserting section 561B (21 U.S.C. 360bbb–0a). New section 561B(d)(1) (21 U.S.C. 360bbb–0a(d)(1)) requires FDA to specify by regulation the deadline of submission of an annual summary of the use of any eligible investigational drug under the Right to Try Act by manufacturers or sponsors, and specifies the contents of such summaries. This section, in conjunction with our general rulemaking authority in section 701(a) of the FD&C Act, serves as our legal authority for this proposed rule.

IV. Description of the Proposed Rule

We are proposing to establish a new subpart D for part 300 of Title 21 of the Code of the **Federal Register**. The proposed rule, if finalized, would specify a deadline for submission of an annual summary of use under the Right to Try Act and identify the contents for that annual summary. Although the Right to Try Act provides that FDA may require the submission of this annual summary in conjunction with the annual report for an applicable investigational drug application for such drug (as required under 21 CFR 312.33), FDA is not proposing to require that the annual summaries be submitted in the annual report. We concluded that a separate process will help to ensure that information about the use of eligible investigational drugs under the Right to Try Act is identified by FDA. We believe sponsors who provide drugs under the Right to Try Act will appreciate this effort to keep the information separate. This approach will also enhance FDA's ability to quickly identify and compile this information so we can post the required annual summary of these reports. For these reasons, we believe that a separate process will be least burdensome overall on FDA, sponsors who provide drugs under the Right to Try Act, and sponsors who do not provide drugs under the Right to Try Act (for whom there will be no obligation to review any changes with respect to the process for annual summaries). We request comment on this assumption.

[1] FDA's Expanded Access Program Information: *https://www.fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm20080392.htm.*

[2] Physicians who have questions should consult with sponsors and manufacturers of eligible investigational drugs. Resources for determining whether there are available clinical trials include the sponsors of an eligible investigational drug or the website *https://www.clinicaltrials.gov/.*

ClinicalTrials.gov Search Results 05/18/2021

	Title	Status	Study Results	Conditions	Interventions	Locations
1	The Safety and Efficacy of Psilocybin in Cancer Patients With Major Depressive Disorder	Recruiting	No Results Available	•Major Depressive Disorder	•Drug: Psilocybin	•Maryland Oncology Hematology PA, Rockville, Maryland, United States
2	Efficacy of Psilocybin in OCD: a Double-Blind, Placebo-Controlled Study.	Recruiting	No Results Available	•Obsessive-Compulsive Disorder	•Drug: Psilocybin (0.25mg/kg) •Drug: Niacin (250mg)	•Connecticut Mental Health Center, New Haven, Connecticut, United States
3	Safety and Efficacy of Psilocybin for Body Dysmorphic Disorder	Recruiting	No Results Available	•Body Dysmorphic Disorders	•Drug: Psilocybin	•New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, United States
4	Effects of Psilocybin in Anorexia Nervosa	Recruiting	No Results Available	•Anorexia Nervosa	•Drug: Psilocybin	•Behavioral Pharmacology Research Unit, Baltimore, Maryland, United States
5	Psilocybin for Depression in People With Mild Cognitive Impairment or Early Alzheimer's Disease	Recruiting	No Results Available	•Depressive Symptoms •Depression •Alzheimer Disease •Mild Cognitive Impairment	•Drug: Psilocybin	•Behavioral Pharmacology Research Unit, Baltimore, Maryland, United States
6	Psilocybin for Treatment of Obsessive Compulsive Disorder	Recruiting	No Results Available	•Obsessive-compulsive Disorder (OCD)	•Drug: Psilocybin 100 mcg/kg •Drug: Psilocybin 300 mcg/kg •Drug: Lorazepam 1 mg	•University of Arizona, Tucson, Arizona, United States
7	Evaluation of Psilocybin in Anorexia Nervosa: Safety and Efficacy	Recruiting	No Results Available	•Anorexia Nervosa	•Drug: Psilocybin	•Altman Clinical and Translational Research Institute, La Jolla, California, United States
8	Psilocybin - Induced Neuroplasticity in the Treatment of Major Depressive Disorder	Recruiting	No Results Available	•Major Depressive Disorder	•Drug: Low Dose Psilocybin •Drug: Placebo •Drug: Medium Dose Psilocybin	•VA Connecticut Healthcare System, West Haven Campus, West Haven, Connecticut, United States
9	The Safety and Efficacy of Psilocybin in Participants With Type 2 Bipolar Disorder (BP-II) Depression.	Recruiting	No Results Available	•Treatment Resistant Depression	•Drug: Psilocybin	•Sheppard Pratt Health System, Baltimore, Maryland, United States
10	An Open Label Study of the Safety and Efficacy of Psilocybin in Participants With Treatment-Resistant Depression (P-TRD)	Recruiting	No Results Available	•Treatment Resistant Depression	•Drug: Psilocybin	•Sheppard Pratt Health System, Baltimore, Maryland, United States
11	Psilocybin Treatment of Major Depressive Disorder With Co-occurring Alcohol Use Disorder	Recruiting	No Results Available	•Major Depressive Disorder •Alcohol Use Disorder	•Drug: Psilocybin •Drug: Placebo	•Johns Hopkins Center for Psychedelic and Consciousness Research, Baltimore, Maryland, United States
12	Effects of Psilocybin in Concussion Headache	Recruiting	No Results Available	•Post-Traumatic Headache	•Drug: Placebo oral capsule •Drug: Low Dose Psilocybin •Drug: High Dose Psilocybin	•VA Connecticut Healthcare System, West Haven, Connecticut, United States
13	Psilocybin-facilitated Treatment for Cocaine Use	Recruiting	No Results Available	•Cocaine-Related Disorders	•Drug: Psilocybin •Drug: Diphenhydramine	•UAB Outpatient Clinical Research Unit, Birmingham, Alabama, United States
14	Pilot Trial of Visual Healing® in Psilocybin-assisted Therapy for Alcohol Use Disorder	Recruiting	No Results Available	•Alcohol Use Disorder	•Drug: Psilocybin plus Visual Healing Set and Setting •Drug: Psilocybin plus Standard Set and Setting	•Pacific Treatment & Research in Psychedelics, Santa Monica, California, United States
15	Pilot RECAP Study in Healthy Normal Volunteers	Recruiting	No Results Available	•Psychedelic Experiences •Amnesia	•Drug: Psilocybin and Midazolam	•UWHealth, 600 Highland Avenue, Madison, Wisconsin, United States
16	Effects of Psilocybin-facilitated Experience on the Psychology and Effectiveness of Professional Leaders in Religion	Recruiting	No Results Available	•Healthy	•Drug: Psilocybin	•Behavioral Biology Research Center, Johns Hopkins Bayview, Baltimore, Maryland, United States
17	Adjunctive Effects of Psilocybin and Buprenorphine	Recruiting	No Results Available	•Opioid Use Disorder	•Drug: Psilocybin with guided counseling	•University of Wisconsin, Madison, Wisconsin, United States

	Title	Status	Study Results	Conditions	Interventions	Locations
18	Psilocybin for the Treatment of Cluster Headache	Recruiting	No Results Available	•Cluster Headache	•Drug: 0.143 mg/kg Psilocybin or 10 mg Psilocybin •Drug: 0.0143 mg/kg Psilocybin or 1 mg Psilocybin •Drug: Placebo	•VA Connecticut Healthcare System, West Haven, Connecticut, United States
19	Psilocybin-facilitated Smoking Cessation Treatment: A Pilot Study	Recruiting	No Results Available	•Nicotine Dependence	•Drug: Psilocybin-assisted treatment •Drug: Nicotine Replacement Therapy (NRT)	•Behavioral Pharmacology Research Unit, Baltimore, Maryland, United States •Neuroimaging Research Branch, NIDA-IRP, Baltimore, Maryland, United States
20	The Safety and Efficacy Of Psilocybin as an Adjunctive Therapy in Participants With Treatment Resistant Depression	Recruiting	No Results Available	•Treatment Resistant Depression	•Drug: Psilocybin	•Kadima Neuropsychiatry Institute, La Jolla, California, United States •Sheaf House, Tallaght Hospital, Dublin, Ireland
21	A Study of Psilocybin for Major Depressive Disorder (MDD)	Recruiting	No Results Available	•Depressive Disorder, Major	•Drug: Psilocybin •Drug: Niacin	•University of California, San Francisco, San Francisco, California, United States •Yale University, New Haven, Connecticut, United States •Segal Trials, Lauderhill, Florida, United States •Great Lakes Clinical Trials, Chicago, Illinois, United States •Johns Hopkins University, Baltimore, Maryland, United States •New York University School of Medicine, New York, New York, United States •University of Wisconsin - Madison, Madison, Wisconsin, United States
22	The Safety and Efficacy of Psilocybin in Participants With Treatment Resistant Depression	Recruiting	No Results Available	•Treatment Resistant Depression	•Drug: Psilocybin	•Kadima Neuropsychiatry Institute, La Jolla, California, United States •Altman Clinical and Translational Research Institute, University of California, San Diego, California, United States •Stanford Department of Psychiatry, Stanford, California, United States •Mood and Anxiety Disorders Program Emory University School of Medicine, Atlanta, Georgia, United States •Ray Worthy Psychiatry LLC, New Orleans, Louisiana, United States •Sheppard Pratt Health System, Baltimore, Maryland, United States •New York State Psychiatric Institute, New York, New York, United States •UT Center of Excellence on Mood Disorders, University of Texas Health Science Center, Houston, Texas, United States •Canadian Rapid Treatment Centre of Excellence, Mississauga, Ontario, Canada •Centre for Addiction and Mental Health, Toronto, Ontario, Canada •and 15 more

	Title	Status	Study Results	Conditions	Interventions	Locations
23	Long Term Follow Up Study to COMP 001 And COMP 003 Trials (P-TRD LTFU)	Recruiting	No Results Available	•Treatment Resistant Depression		•Kadima Neuropsychiatry Institute, La Jolla, California, United States •Altman Clinical and Translational Research Institute, University of California, San Diego, California, United States •Mood and Anxiety Disorders Program Emory University School of Medicine, Atlanta, Georgia, United States •UT Center of Excellence on Mood Disorders, University of Texas Health Science Center, Houston, Texas, United States •National Institute of Mental Health Czech Republic, Klecany, Czechia •Sheaf House, Tallaght Hospital, Dublin, Ireland •Groningen University Medical Centre, Groningen, Netherlands •Kings College London, Institute of Psychiatry, Psychology and Neurology, London, United Kingdom

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Expanded Access and Right to Try: Access to Investigational Drugs

Updated March 16, 2021

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CRS REPORT
Prepared for Members and Committees of Congress

Congressional Research Service
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Expanded Access and Right to Try: Access to Investigational Drugs

SUMMARY

R45414

March 16, 2021

Agata Bodie
Analyst in Health Policy

The Food and Drug Administration (FDA) regulates the safety and effectiveness of drugs and biological products under its authorities in the Federal Food, Drug and Cosmetic Act (FFDCA) and Public Health Service Act (PHSA). In general, a manufacturer may not sell a drug or biologic in the United States until FDA has reviewed and approved its marketing application (i.e., a new drug application [NDA] or biologics license application [BLA]).

The primary route for an individual to obtain an investigational (i.e., unapproved) drug is to enroll in a clinical trial testing that new drug. However, an individual may be excluded from the clinical trial because its enrollment is limited to patients with particular characteristics (e.g., in a particular stage of a disease, with or without certain other conditions, or in a specified age range), or because the trial has reached its target enrollment number. In certain circumstances, FDA may allow an individual to obtain an investigational drug outside of a clinical trial through its expanded access procedures. Another option, the pathway created by the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017 ("Right to Try Act," P.L. 115-176), does not require FDA permission.

Right to Try Act

The Right to Try Act became federal law on May 30, 2018. Prior to its passage, 40 states had enacted related legislation. The goal of these legislative efforts was to allow individuals with imminently life-threatening diseases or conditions to seek access to investigational drugs directly from the manufacturer without the step of procuring permission from FDA. Another goal—held by the Goldwater Institute, which led the initiative toward state bills, and some of the legislative proponents—was focused more on the process: to eliminate government's role in an individual's choice.

The Right to Try Act offers eligible individuals and their physicians a pathway other than FDA's expanded access procedures to obtain investigational drugs. It defines an *eligible patient* as one who (1) has been diagnosed with a life-threatening disease or condition, (2) has exhausted approved treatment options and is unable to participate in a clinical trial involving the eligible investigational drug (as certified by a physician who meets specified criteria), and (3) has given written informed consent regarding the drug to the treating physician.

It defines an *eligible investigational drug* as an investigational drug (1) for which a Phase 1 clinical trial has been completed, (2) that FDA has not approved or licensed for sale in the United States for any use, (3) that is the subject of an NDA or BLA pending FDA decision or is the subject of an active investigational new drug application and is being studied in a clinical trial that is intended to support the drug's effectiveness, and (4) for which the manufacturer has not discontinued active development or production and for which the FDA has not placed on clinical hold.

The Right to Try Act also has provisions that limit how the Secretary of Health and Human Services (through the FDA) can use data regarding clinical outcomes of patients who get these drugs through this pathway; require a drug's sponsor or manufacturer to report annually to FDA on use of the pathway; and require FDA to post certain annual summaries. Finally, the Right to Try Act states that the sponsor or manufacturer has "no liability" for actions under these provisions. The no-liability provision applies also to a prescriber, dispenser, or "other individual entity" unless there is "reckless or willful misconduct, gross negligence, or an intentional tort."

Before the Right to Try Act was enacted, observers discussed several obstacles to access to investigational drugs through FDA's expanded access procedures. These included some that were FDA-related: the reportedly difficult process to request FDA permission, concern about FDA use of adverse event data, and the role of FDA as gatekeeper. Some related to why a manufacturer might decline to provide an investigational drug: limited available supply, liability, limited staff and facility resources, and concerns about use of outcomes data. The Right to Try Act directly eliminates some of these concerns, addresses some others, and leaves others unaddressed.

Opponents of the law have expressed concern about the erosion of protections for patients who may be exposed to drugs that are unsafe or ineffective. For example, in taking FDA out of the equation, the Right to Try Act limits the agency's ability to make suggestions to the protocols under which investigational drugs are provided, potentially compromising patient safety.

Congressional Considerations

While the Right to Try Act aimed to remove certain perceived obstacles to obtaining investigational drugs, unknowns remain regarding its impact on patients, drug manufacturers, and FDA. These unknowns include (1) whether more patients have received investigational drugs than prior to the law's enactment, (2) whether manufacturers are granting more requests for investigational drugs under the Right to Try Act pathway than previously under expanded access, and (3) FDA's role in implementing certain Right to Try Act requirements when the purpose of the law was to remove FDA from the situation. Congress may consider whether the law has had the effect its sponsors intended or whether legislative changes are necessary.

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Introduction

The Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017 ("Right to Try Act," P.L. 115-176) became federal law on May 30, 2018. Prior to its passage, 40 states had enacted related legislation. The law's goal was to allow individuals with imminently life-threatening diseases or conditions to seek access to investigational drugs without the step of procuring permission from the Food and Drug Administration (FDA). Another goal—held by the Goldwater Institute, which led the initiative toward state bills, and some of the legislative proponents—was focused more on the process: to eliminate government's role in an individual's choice.[1]

The effort to publicize the issue and press for a federal solution involved highlighting the poignant situations of individuals who sought access. For example, in March 2014, millions of Americans heard about the plight of a seven-year-old boy with cancer. He was battling an infection following a bone marrow transplant that no antibiotic had been able to treat.[2] His physicians thought an experimental antiviral drug might help. Because FDA had not yet approved that experimental drug, it was not available in pharmacies. FDA did have the authority to permit the use of an unapproved drug in certain circumstances—a process referred to as *expanded access*. For FDA to grant that permission, however, the manufacturer must have agreed to provide the drug. The manufacturer, which was still testing the drug, declined. Other stories often pointed toward FDA as an obstacle.

During this time, certain groups—for example, the Goldwater Institute—encouraged Congress to act on right-to-try legislation (i.e., legislation that would allow patients to access investigational drugs without FDA permission). The institute framed the issue as one of individual freedom and circulated model legislation.[3] After 33 states[4] enacted legislation reflecting the Goldwater Institute-provided model bill, in January 2017, some Members of Congress introduced a bill to try to address the issue. The Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017—named for several individuals facing amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) or Duchenne muscular dystrophy—sought to remove what proponents saw as FDA obstacles to patient access. On May 30, 2018, President Trump signed the bill into law (P.L. 115-176).

This report discusses

[1] Goldwater Institute, "President Trump Signs Right to Try Act into Law," May 30, 2018, https://goldwaterinstitute.org/article/president-trump-signs-right-to-try-act-into-law/. The Goldwater Institute's website describes itself as "a leading free-market public policy research and litigation organization that is dedicated to empowering all Americans to live freer, happier lives … the Institute focuses on advancing the principles of limited government, economic freedom, and individual liberty" (Goldwater Institute, https://goldwaterinstitute.org/about/).

[2] Steve Usdin, "Josh Hardy chronicles: How Chimerix, FDA grappled with providing compassionate access to Josh Hardy," *BioCentury*, March 31, 2014, https://www.biocentury.com/biocentury/regulation/2014-03-31/how-chimerix-fda-grappled-providing-compassionate-access-josh-hardy; Kim Painter, "Drug company changes course, gives drug to sick boy," *USA Today*, March 12, 2014, http://www.usatoday.com/story/news/nation/2014/03/11/chimerix-josh-hardy-drug/6308891/; and David Kroll, "Josh Hardy Going Home After Getting Chimerix Anti-Viral Drug," *Forbes*, July 17, 2014, http://www forbes.com/sites/davidkroll/2014/07/17/josh-hardy-going-home-after-getting-chimerix-anti-viral-drug/.

[3] Goldwater Institute, "Right to Try Model Legislation," https://goldwaterinstitute.org/wp-content/uploads/cms_page_media/2016/1/5/GoldwaterInstituteRighttoTryModel.pdf.

[4] Starlee Coleman, "Ohio becomes 33rd state to adopt right to try law for terminally ill," Goldwater Institute, January 5, 2017, https://goldwaterinstitute.org/article/ohio-33rd-state-to-adopt-right-to-try-law-terminally-ill/.

- how FDA regulates investigational drugs;
- FDA's expanded access procedures and the perceived obstacles to individuals accessing experimental drugs through this mechanism;
- a summary of the provisions in the Right to Try Act and how they are meant to address those obstacles; and
- selected provisions in the Right to Try Act and what questions remain unresolved.

FDA Regulation of Investigational Drugs

The FDA regulates the safety and effectiveness of drugs and biological products ("biologics") under its authorities in the Federal Food, Drug and Cosmetic Act (FFDCA) and Public Health Service Act (PHSA).[5] In general, a manufacturer may not sell a drug or biologic in the United States until FDA has reviewed and approved its marketing application (i.e., a new drug application [NDA] or biologics license application [BLA]). That application for a new drug or biologic must include data from clinical trials as evidence of the product's safety and effectiveness for its stated purpose(s).[6]

After laboratory and animal studies have identified a potential drug or biologic, the sponsor of the clinical trial, usually its manufacturer, may submit an investigational new drug (IND) application to FDA for permission to begin testing the drug in humans.[7] An IND must include information about the proposed study design, chemistry and manufacturing of the drug, and the investigator's qualifications, among other information.[8] The investigator also must provide assurance that an Institutional Review Board (IRB) will provide initial and continuous review and approval of each of the studies in the clinical investigation to ensure that participants are aware of the drug's investigative status and that any risk of harm will be necessary, explained, and minimized.[9] Sponsors of clinical trials also must comply with FDA regulations governing protection of human subjects (e.g., informed consent),[10] adverse event reporting,[11] and charging for investigational new drugs,[12] among other requirements.

FDA has 30 days to review an IND, after which a sponsor may begin clinical testing if the agency has not objected and imposed a clinical hold.[13] In reviewing an IND, FDA's primary objective is to assure the safety and rights of human subjects, and with respect to Phase 2 and 3 trials

[5] Whereas the FFDCA (§505) authorizes FDA to approve and regulate drugs, the Public Health Service Act (PHSA §351) authorizes FDA to license biological products (e.g., monoclonal antibodies, vaccines). Most FDA procedures regarding drugs also apply to the agency's regulation of biological products.

[6] FFDCA §505(b) [21 U.S.C. §355(b)], PHSA §351(a) [42 U.S.C. §262(a)], 21 C.F.R. §314.50, §601.2. For an overview of the general process of drug approval in the United States, see CRS Report R41983, *How FDA Approves Drugs and Regulates Their Safety and Effectiveness*. See, also, FDA, "How Drugs are Developed and Approved," http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default htm.

[7] FFDCA §505(i) [21 U.S.C. §355(i)], PHSA §351(a)(3) [42 U.S.C. §262(a)(3)], 21 C.F.R. Part 312.

[8] 21 C.F.R. §312.23.

[9] 21 C.F.R. §312.23(a)(1)(iv) and 21 C.F.R. Part 56.

[10] 21 C.F.R. Part 50.

[11] 21 C.F.R. §312.32.

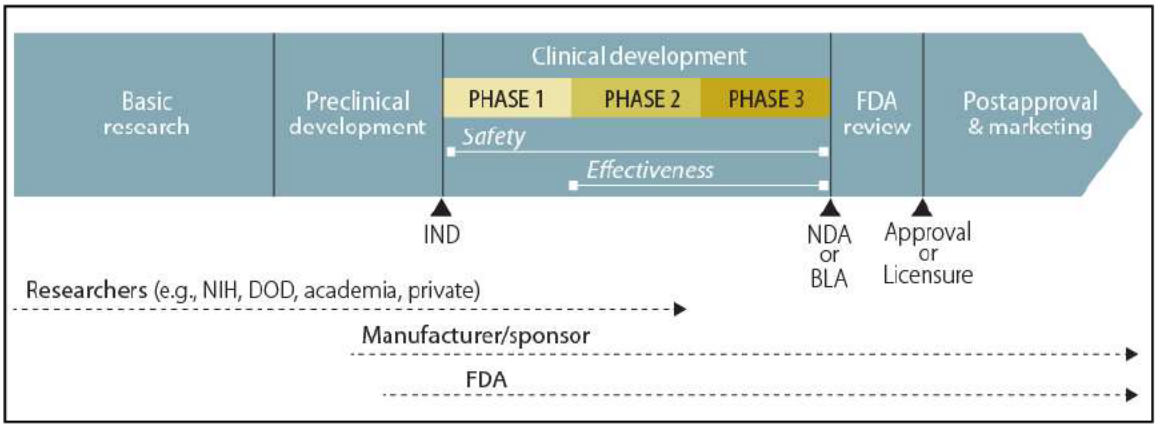
[12] 21 C.F.R. §312.8.

[13] 21 C.F.R. §312.20(c).

specifically, to ensure that the quality of the scientific investigations and evaluations is adequate to permit an evaluation of the drug's safety and effectiveness.[14]

Once the IND application is approved, the sponsor may then start the first of three major phases of clinical—human—trials. (**Figure 1** illustrates the general path of a pharmaceutical product.) Researchers first test in a small number of human volunteers the *safety* they had previously demonstrated in animals. These trials, called Phase 1 clinical trials, attempt "to determine dosing, document how a drug is metabolized and excreted, and identify acute side effects."[15] If a sponsor considers the product still worthy of investment based on the results of a Phase 1 trial, it continues with Phase 2 and Phase 3 trials. Those trials look for evidence of the product's *effectiveness*—how well it works for individuals with the particular characteristic, condition, or disease of interest.[16] Phase 2 is a first attempt at assessing effectiveness and its experience helps to plan the subsequent Phase 3 clinical trial, which the sponsor designs to be large enough to statistically test for meaningful differences attributable to the drug.

Figure 1. Standard Drug Development Path



Source: Created by CRS.

Notes: The figure does not show the elements of the path to scale.
BLA = biologics license application. DOD = Department of Defense. FDA = Food and Drug Administration. IND = investigational new drug application. NDA = new drug application. NIH = National Institutes of Health.

The primary route for an individual to obtain an investigational drug is to enroll in a clinical trial testing that new drug. However, an individual may be excluded from the clinical trial because its enrollment is limited to patients with particular characteristics (e.g., in a particular stage of a disease, with or without certain other conditions, or in a specified age range), or because the trial has reached its target enrollment number. In certain circumstances, FDA may allow an individual to obtain an investigational drug outside of a clinical trial through its expanded access procedures. Another option, the pathway created by the Right to Try Act, does not require permission from FDA. **Table 1** summarizes selected differences in criteria for access to investigational drugs through participation in clinical trials, expanded access, and right to try.[17]

[14] 21 C.F.R. §312.22(a).

[15] FDA, "Inside Clinical Trials: Testing Medical Products in People," http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143531.htm.

[16] 21 C.F.R. §312.21(b) & (c).

[17] Under certain emergency circumstances, FDA may issue an emergency use authorization (EUA) to allow the use of an unapproved medical product or the unapproved use of an approved product. The EUA mechanism is beyond the

Table 1. Access to Investigational Drugs

Clinical Trials, Expanded Access, and Right to Try

	Clinical Trials	Expanded Access	Right to Try
Who is eligible?	Individual who meets the trial's requirements for inclusion and exclusion	Individual must have a serious or *immediately* life-threatening disease or condition, be unable to participate in a clinical trial, and have no comparable therapeutic options	Individual must have a serious or life-threatening disease or condition, be unable to participate in a clinical trial, and have exhausted approved treatment options
When can patients gain access?	May enroll in Phase 1, 2, or 3 trials	During or after Phase 1, 2, or 3 trials	After Phase 1 trials have been completed
Who must provide permission?	FDA, IRB, and drug manufacturer	FDA, IRB, and drug manufacturer	Drug manufacturer
Is informed consent from the individual required?	Yes, in accord with 21 C.F.R. Part 50 "Protection of Human Subjects"	Yes, in accord with 21 C.F.R. Part 50	Yes, but not defined and exempt from 21 C.F.R. Part 50

Source: FFDCA §§561 & 561B, 21 C.F.R. §312.305, FDA, "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers," Guidance for Industry, June 2016, updated October 2017, https://www.fda.gov/media/85675/download.

Expanded Access and Obstacles

FDA Requirements

The primary purpose of expanded access is to provide investigational drugs as treatment for patients who lack therapeutic alternatives. This is in contrast to clinical trials, which are designed primarily to generate evidence of safety and effectiveness to support approval of an NDA or BLA.[18]

Through FDA's expanded access procedure, a person, acting through a licensed physician, may request access to an investigational drug—through either a new IND or a revised protocol to an existing IND—if[19]

- a *licensed physician* determines (1) the patient has "no comparable or satisfactory alternative therapy available to diagnose, monitor, or treat" the serious disease or condition; and (2) "the probable risk to the person from the investigational drug

scope of this report but is discussed in other CRS products. See, for example, CRS In Focus IF10745, *Emergency Use Authorization and FDA's Related Authorities*.

[18] FDA, "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers," Guidance for Industry, June 2016, updated October 2017, pp. 2-3, https://www.fda.gov/media/85675/download.

[19] FFDCA §561(b) [21 U.S.C. §360bbb(b)]. See, also, FDA, "Expanded Access: Information for Patients," https://www fda.gov/NewsEvents/PublicHealthFocus/ExpandedAccessCompassionateUse/ucm20041768 htm. In addition to the individual IND or protocol, regulations describe other categories of expanded use of investigational drugs: intermediate-size patient populations, with one IND or protocol that consolidates several individual access requests, and treatment IND or treatment protocol for "widespread treatment use" when a drug is farther along the clinical trial and marketing application process. See FFDCA §561(c) [21 U.S.C. §360bbb(c)]; and 21 C.F.R. §§312.305, 312.310, 312.315, and 312.320.

or investigational device is not greater than the probable risk from the disease or condition";

- the *Secretary* (FDA, by delegation of authority) determines (1) "that there is sufficient evidence of safety and effectiveness to support the use of the investigational drug" for this person; and (2) "that provision of the investigational drug ... will not interfere with the initiation, conduct, or completion of clinical investigations to support marketing approval"; and
- the *sponsor* of the investigational drug, or clinical investigator, submits to FDA a clinical protocol consistent with the requirements of FFDCA Section 505(i) and related regulations.

FDA makes most expanded access IND and protocol decisions on an individual-case basis. Consistent with the IND process under which the expanded access mechanism falls, it considers the requesting physician as the investigator. The investigator must comply with informed consent and IRB review of the expanded use.[20] The sponsor of the IND must make required safety reports to FDA.[21] FDA may permit a sponsor to charge a patient for the investigational drug, but "only [for] the direct costs of making its investigational drug available"[22] (i.e., not for development costs or profit).

Expanded access could apply outside of the clinical trial arena in these situations:

> (1) use in situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage of the approved drug; (3) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug under the REMS; or (4) use for other reasons.[23]

Obstacles to Access

The widespread use of expanded access is limited by an important factor: whether the manufacturer agrees to provide the drug, which—because it is not FDA-approved—cannot be obtained otherwise. FDA does not have the authority to compel a manufacturer to participate. In addition, some manufacturers have expressed concern regarding how FDA would use adverse event data from expanded access when reviewing drug applications. Many highly publicized accounts of specific individuals' struggles with life-threatening conditions and efforts by activists influenced public debate over access. Examples of public attitudes included news accounts of specific individuals' struggles with life-threatening conditions. Some found the process of asking FDA for a treatment IND too cumbersome. Others questioned FDA's right to act as a gatekeeper

[20] 21 C.F.R. §312.305(c)(4).

[21] 21 C.F.R. §312.305(c)(5).

[22] 21 C.F.R. §312.8 and FDA, "Guidance for Industry: Charging for Investigational Drugs Under an IND—Questions and Answers," Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research, June 2016, https://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm351264.pdf.

[23] FDA, "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers," Guidance for Industry, June 2016, updated October 2017, p. 3, https://www.fda.gov/media/85675/download.

at all.[24] Some pointed to manufacturers' refusal to provide their experimental drugs.[25] Most critics, therefore, see solutions as within the control of FDA or pharmaceutical companies. This section lays out key perceived obstacles and issues—both FDA- and manufacturer-related—with respect to expanded access prior to the enactment of the Right to Try Act.

FDA-Related Issues

Difficult Process to Request FDA Permission

In February 2015, FDA issued draft guidance (finalized in June 2016 and updated in October 2017) on individual patient expanded access applications, acknowledging difficulties with requesting permission for access to investigational drugs from the agency.[26] FDA developed a new form that a physician could use when requesting expanded access for an individual patient. It reduced the amount of information required from the physician by allowing reference (with the sponsor's permission) to the information the sponsor had already submitted to FDA in its IND.[27]

In October 2017, FDA modified its expanded access IRB review policy to allow one IRB member to concur with the treatment use rather than the full IRB.[28] This policy change was made pursuant to a statutory directive that FDA streamline IRB review of individual patient expanded access requests.[29] A September 2019 report published by the Government Accountability Office (GAO) found that the IRB update was helpful for physicians and patients, for example, by reducing the amount of time for patients to obtain access to investigational drugs.[30]

In instances where a patient needs emergency treatment with the investigational product before a physician can submit a written request, FDA can authorize expanded access for an individual patient by phone or email, and the physician or sponsor must agree to submit an IND or protocol

[24] The Abigail Alliance, formed by the father of a young woman with cancer who had unsuccessfully attempted to get an investigational drug, subsequently went to court, claimed "as a fundamental aspect of constitutional due process, the right to choose to take medication of unknown benefit and risk that might potentially be lifesaving" (Linda Greenhouse, "Justices Won't Hear Appeal on Drugs for Terminally Ill," *New York Times*, January 15, 2008, http://www.nytimes.com/2008/01/15/washington/15appeal.html?_r=0). The U.S. Court of Appeals for the District of Columbia Circuit 2007 opinion found "that there is no Constitutional right to access to experimental drugs for terminally ill patients"; in 2008, the Supreme Court declined to consider an appeal (FDA, "Court Decisions, Fiscal Year 2008," http://www fda.gov/downloads/iceci/enforcementactions/enforcementstory/ucm129820.pdf).

[25] Jonathan J. Darrow, Ameet Sarpatwari, Jerry Avorn, M.D., and Aaron S. Kesselheim, "Practical, Legal, and Ethical Issues in Expanded Access to Investigational Drugs," *New England Journal of Medicine*, January 2015, vol. 372, pp. 279-286.

[26] FDA, "Individual Patient Expanded Access Applications: Form FDA 3926," Guidance for Industry, June 2016, Updated October 2017, p. 4, https://www fda.gov/media/91160/download.

[27] FDA estimated that it would take a physician about 45 minutes to complete the proposed new form rather than the 8 hours estimated for the original form (or 16 hours when the request was for emergency access) (80 FR 7318). FDA, "Guidance for Industry: Individual Patient Expanded Access Applications: Form FDA 3926."

[28] FDA, "Statement from FDA Commissioner Scott Gottlieb, M.D., on new efforts to strengthen FDA's expanded access program," November 8, 2018, https://www fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-efforts-strengthen-fdas-expanded-access-program. FDA, "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers," Guidance for Industry, p. 6.

[29] P.L. 115-52, §610(b).

[30] GAO, "Investigational Drugs: FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients," GAO-19-630, September 2019, pp. 18-19, https://www.gao.gov/assets/710/701243.pdf.

within 15 working days.[31] In such emergency circumstances, treatment with the investigational drug may begin prior to IRB approval, but the IRB must be notified within five working days.[32]

Coincident with discussions preceding passage of the Right to Try Act, FDA had commissioned an independent report on its expanded access program. Citing that report,[33] in November 2018, then-FDA Commissioner Gottlieb announced several actions to improve its program.[34] These included an enhanced webpage to help applicants navigate the application process and establishing an agency-wide Expanded Access Coordinating Committee. In July 2019, FDA launched the Oncology Center of Excellence Project Facilitate, which provides a single point of contact through which FDA oncology staff help physicians through the process of submitting an expanded access request for an individual patient with cancer.[35] According to a 2019 GAO report, officials from one drug manufacturer indicated that Project Facilitate may help reduce the burden on oncologists seeking expanded access to investigational drugs for their patients. However, other officials from the same manufacturer "raised concerns about the potential for FDA to intentionally or unintentionally pressure companies to make their investigational drugs available to patients, should FDA have increased involvement with drug manufacturers as part of the pilot program."[36]

Use of Adverse Event Data from Expanded Access

In October 2017, FDA updated its guidance to address how the agency reviews adverse event data in the expanded access context. In the guidance, FDA explains that reviewers are aware of the context in which adverse event data are generated—for example, that patients who receive a drug through expanded access may have a more advanced stage of the disease than those enrolled in a clinical trial—and evaluate adverse events in that context. The guidance further states that "FDA is not aware of instances in which adverse event information from expanded access has prevented FDA from approving a drug."[37] However, FDA officials have indicated to GAO that "efficacy and safety data from the expanded access program have been used to support drug approvals in several instances."[38] Further, expanded access use may allow for the detection of rare adverse events or may contribute to information about use of the drug in certain populations that are not exposed to the drug in clinical trials.[39] While some drug manufacturers have indicated that they

[31] 21 C.F.R. §312.310(d). FDA "For Physicians: How to Request Single Patient Expanded Access ("Compassionate Use")," https://www.fda.gov/drugs/investigational-new-drug-ind-application/physicians-how-request-single-patient-expanded-access-compassionate-use.

[32] FDA, "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers," Guidance for Industry, p. 5.

[33] FDA, "Expanded Access Program Report," May 2018, https://www fda.gov/media/119971/download.

[34] FDA, "Statement from FDA Commissioner Scott Gottlieb, M.D., on new efforts to strengthen FDA's expanded access program," November 8, 2018, https://www fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-new-efforts-strengthen-fdas-expanded-access-program.

[35] FDA, "Project Facilitate," https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate. GAO, "Investigational Drugs: FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients," pp. 18-19.

[36] GAO, "Investigational Drugs: FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients," p. 19.

[37] FDA, "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers," Guidance for Industry, p. 18.

[38] GAO, "Investigational Drugs: FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients," p. 22.

[39] FDA, "Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers," Guidance for

view FDA's updated guidance as an improvement, others maintained that they still had significant concerns about adverse event data from expanded access use negatively affecting development of their investigational new drugs.[40]

FDA as Gatekeeper

FDA action is not the final obstacle to access, as the manufacturer still needs to agree to provide their product. Between FY2010 through FY2020, FDA received 16,380 expanded access requests and granted 16,258 (99.3%) of them.[41]

Leading up to passage of the Right to Try Act, in August 2014, a *USA Today* editorial had called the FDA procedures that patients must follow for compassionate use access "bureaucratic absurdity," "daunting," and "fatally flawed." Echoing much of the criticism that FDA had received regarding the issue, it called for one measure that would "cut out the FDA, which now has final say."[42] The solution the editorial proposed involved what proponents term "right to try" laws. By spring 2018, 40 states had passed right to try laws in the absence of federal legislation.[43] The laws varied on the detail required in informed consent and liability issues of the manufacturer and the patient's estate.[44] However, several experts had suggested that this state law approach is unlikely to directly increase patient access.[45] Before passage of the federal Right to Try Act, analysts raised questions about how federal law (the FFDCA), which required FDA approval of such arrangements, might preempt this type of state law.[46] After the enactment of the federal Right to Try Act, some legal analysts had predicted that the issue of federal preemption of state laws would "likely be determined on a case-by-case basis."[47]

Industry, p. 18.

[40] GAO, "Investigational Drugs: FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients," pp. 21-22.

[41] Reports for 2010 through 2020 are at FDA, "Expanded Access INDs and Protocols," https://www fda.gov/drugs/ind-activity/expanded-access-inds-and-protocols.

[42] The Editorial Board, "FDA vs. right to try: Our view," *USA Today*, August 17, 2014, http://www.usatoday.com/story/opinion/2014/08/17/ebola-drugs-terminally-ill-right-to-try-editorials-debates/14206039/.

[43] National Conference of State Legislatures, "'Right to Try' Experimental Prescription Medicines State Laws and Legislation for 2014-2017," March 7, 2018, http://www ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx#Right_to_Try.

[44] For example: House Bill 14-1281, State of Colorado, Sixty-ninth General Assembly, http://www.leg.state.co.us/clics/clics2014a/csl nsf/fsbillcont/CE8AAA4FAF92567487257C6F005C8D97?Open&file=1281_enr.pdf; House Bill No. 891, Enrolled, Louisiana, https://www.legis.la.gov/Legis/ViewDocument.aspx?d=902583; Conference Committee Substitute No. 2 for Senate Substitute for House Committee Substitute for House Bill No. 1685, Truly Agreed To and Finally Passed, Missouri, 97th General Assembly, 2014, http://www house.mo.gov/billtracking/bills141/billpdf/truly/HB1685T.PDF; Public Act Numbers 345 and 346 of 2014, State of Michigan, 97th Legislature, http://www.legislature mi.gov/(S(gb2onn55vxkuylrvqmn3axrp))/mileg.aspx?page=PublicActs.

[45] Arthur Caplan, "Bioethicist: 'Right to Try' Law More Cruel Than Compassionate," NBC NEWS, May 18, 2014, http://www.nbcnews.com/health/health-news/bioethicist-right-try-law-more-cruel-compassionate-n108686; and David Kroll, "The False Hope Of Colorado's 'Right To Try' Investigational Drug Law," *Forbes*, May 19, 2014, http://www.forbes.com/sites/davidkroll/2014/05/19/the-false-hope-of-colorados-right-to-try-act/.

[46] See, generally, Elizabeth Richardson, "Health Policy Brief: Right-to-Try Laws," *Health Affairs*, March 5, 2015, http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=135.

[47] Phoebe Mounts, Kathleen Sanzo, and Jacqueline Berman, "A Closer Look At New Federal 'Right To Try' Law," Law 360, June 1, 2018, https://www.law360.com/articles/1048871/a-closer-look-at-new-federal-right-to-try-law.

Manufacturer-Related Issues

The manufacturer faces a complex decision in determining whether or not to give its experimental drug to a patient who requests it. In making a decision in each case, the manufacturer considers available supply of the drug, liability, safety, and whether adverse event or outcome data will affect FDA's consideration of a new drug application in the future.

Available Supply

If a manufacturer has only a tiny amount of an experimental drug, that paucity may limit distribution, no matter what the manufacturer would like to do.[48] Sponsors of early clinical research make small amounts of experimental products for use in small Phase 1 safety trials, and progressively more for Phase 2 and 3 trials. Although one or two additional patients may not cause supply problems, a manufacturer does not know how many expanded access requests it will receive. Investment in building up to large-scale production usually comes only after reasonable assurance that the product will get FDA approval. For a company to redirect its current manufacturing capacity involves financial, logistic, and public relations decisions.

Liability

In discussing expanded access, some manufacturers have raised liability concerns if patients report injury from the investigational products.[49] Whether these concerns become illustrated by court cases and how any issues may be resolved in future laws are beyond the scope of this discussion.[50]

Limited Staff and Facility Resources

Any energy put into setting up and maintaining an expanded access program could take away from a company's focus on completing clinical trials, preparing an NDA, and launching a product into the market. While this delay would have bottom-line implications, one CEO, in denying expanded access, portrayed the decision as an equity issue, saying, "We held firm to the ethical standard that, were the drug to be made available, it had to be on an equitable basis, and we couldn't do anything to slow down approval that will help the hundreds or thousands of [individuals]." Pointing to ways granting expanded access might divert them from research tasks and postpone approval, he said, "Who are we to make this decision?"[51]

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[48] GAO, "Investigational Drugs: FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients," p. 25.

[49] For example, see Sam Adriance, "Fighting for the 'Right To Try' Unapproved Drugs: Law as Persuasion," *Yale Law Journal Forum*, vol. 124, December 4, 2014, http://www.yalelawjournal.org/forum/right-to-try-unapproved-drugs; Darshak Sanghavi, Meaghan George, and Sara Bencic, "Individual Patient Expanded Access: Developing Principles For A Structural And Regulatory Framework," *Health Affairs Blog*, July 31, 2014, http://healthaffairs.org/blog/2014/07/31/individual-patient-expanded-access-developing-principles-for-a-structural-and-regulatory-framework/; and Elizabeth Richardson, "Health Policy Brief: Right-to-Try Laws," *Health Affairs*, March 5, 2015, http://www.healthaffairs.org/healthpolicybriefs/brief.php?brief_id=135.

[50] CRS Legal Sidebar LSB10115, *Federal "Right-to-Try" Legislation: Legal Considerations*.

[51] Steve Usdin, "Josh Hardy chronicles: How Chimerix, FDA grappled with providing compassionate access to Josh Hardy," BioCentury, March 31, 2014, https://www.biocentury.com/biocentury/regulation/2014-03-31/how-chimerix-fda-grappled-providing-compassionate-access-josh-hardy.

Data for Assessing Safety and Effectiveness

By distributing the drug outside a carefully designed clinical trial, it may be difficult, if not impossible, to collect the data that would validly assess safety and effectiveness. Clinical trials are structured to assess the safety of a drug as well as its effectiveness. The trial design may exclude subjects who are so ill from either the disease or condition for which the drug is being tested or another disease or condition. This allows, among other reasons, the analysis of adverse events in the context of the drug and disease of interest. The patients who would seek a drug under a right to try pathway are likely to be very ill and likely to experience serious health events. Those events could be a result of the drug or those events could be unrelated. They would present difficulties both scientific and public relations-wise to the manufacturer. A manufacturer may avoid those risks by choosing to not provide a drug outside a clinical trial.

As mentioned, FDA has indicated that it is not aware of any instances in which safety and effectiveness data obtained from expanded access have prevented approval of a drug, but there are instances in which such data have been used to support approval (see the section "Use of Adverse Event Data from Expanded Access").

Disclosure

It is unclear how many people request and are denied expanded access to experimental drugs by manufacturers. This lack of information makes devising solutions to manufacturer-based obstacles difficult. Although FDA reports the number of requests it receives, manufacturers do not (nor does FDA require them to do so). The number of individuals who approach manufacturers is unknown.

In December 2016, the 21st Century Cures Act amended the FFDCA to require a manufacturer or distributor of an investigational drug intended for a serious disease or condition to make its policies on evaluating and responding to compassionate use requests publicly available.[52] However, the law does not require manufacturers to disclose how many requests they receive, grant, or deny.

A 2019 GAO study surveyed 29 drug manufacturers regarding their policies for individual patient access to investigational drugs.[53] Of those surveyed, 23 reported using their websites to communicate whether they considered individual requests for access to investigational drugs outside of clinical trials; the remaining 6 were in the process of developing this content for their websites. Of those 23 manufacturers, 19 stated they were willing to consider requests, while 4 stated they were not. Of the 19 drug manufacturers willing to consider requests, 13 indicated that they require the relevant regulatory authority to review requests, of which 6 specified that they require FDA to review requests for access in the United States.

The Right to Try Act

On January 24, 2017, Senator Johnson introduced S. 204, the Trickett Wendler Right to Try Act of 2017, and the bill had 43 cosponsors at that time. On August 3, 2017, the Senate Committee on Health, Education, Labor, and Pensions discharged the bill by unanimous consent. The same day,

[52] FFDCA §561A [21 U.S.C. §360bbb-0], as added by P.L. 114-255, §3032.

[53] GAO, "Investigational Drugs: FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients," pp. 24-26.

the Senate passed S. 204, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act (P.L. 115-176) with a substantial amendment also by unanimous consent.

On March 13, 2018, Representative Fitzpatrick introduced a related bill, H.R. 5247, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2018, and the bill had 40 cosponsors at that time. On March 21, the House passed the bill (voting 267-149). The House accepted the Senate bill on May 22, 2018 (voting 250-169), and President Trump signed it into law on May 30, 2018.

This section of the report first summarizes the provisions in the Right to Try Act. It then discusses how those provisions address some of the obstacles described in the previous section.

Provisions in the Right to Try Act

The Right to Try Act added FFDCA Section 561B, Investigational Drugs for Use by Eligible Patients. It has a separate paragraph that is not linked to an FFDCA section to limit the liability to all entities involved in providing an eligible drug to an eligible patient. It concludes with a "Sense of the Senate" section.

FFDCA Section 561B has several provisions that mirror many steps in FDA's expanded access program. A major difference is that the new section is designed to exist wholly outside the jurisdiction and participation of FDA. These provisions

- define an *eligible patient* as one who (1) has been diagnosed with a life-threatening disease or condition, (2) has exhausted approved treatment options and is unable to participate in a clinical trial involving the eligible investigational drug (as certified by a physician who meets specified criteria), and (3) has given written informed consent regarding the drug to the treating physician;[54]
- define an *eligible investigational drug* as an investigational drug (1) for which a Phase 1 clinical trial has been completed, (2) that FDA has not approved or licensed for sale in the United States for any use, (3) that is the subject of an NDA or BLA pending FDA decision or is the subject of an active IND and is being studied in a clinical trial that is intended to form the primary basis of the drug's effectiveness, and (4) for which the manufacturer has not discontinued active development or production and which the FDA has not placed on clinical hold;[55] and
- exempt use under this section from parts of the FFDCA and FDA regulations regarding misbranding, certain labeling and directions for use, drug approval, investigational new drug regulations, protection of human subjects, and IRBs.[56]

FFDCA Section 561B includes provisions that address use of clinical outcomes and reporting of certain information to FDA. These provisions

- prohibit the Secretary (FDA) from using clinical outcome data related to use under this section "to delay or adversely affect the review or approval of such drug" unless the FDA determines its use is "critical to determining [its] safety," at which time the FDA must provide written notice to the sponsor to include a

[54] FFDCA §561B(a)(1) [21 U.S.C. §360bbb-0a(a)(1)].

[55] FFDCA §561B(a)(2) [21 U.S.C. §360bbb-0a(a)(2)].

[56] FFDCA §561B(b) [21 U.S.C. §360bbb-0a(b)].

public health justification, or unless the sponsor requests use of such clinical outcome data;[57]

- require the sponsor to submit an annual summary to FDA to include "the number of doses supplied, the number of patients treated, the uses for which the drug was made available, and any known serious adverse events";[58] and
- require FDA to post an annual summary on its website to include the number of drugs for which (1) FDA determined the need to use clinical outcomes in the review or approval of an investigational drug, (2) the sponsor requested that clinical outcomes be used, and (3) the clinical outcomes were not used.[59]

The act has an uncodified section titled "No Liability," which does not correspond to the FDA's expanded access program. The provision states that, related to use of a drug under the new FFDCA Section 561B,

- "no liability in a cause of action shall lie against … a sponsor or manufacturer; or … a prescriber, dispenser, or other individual entity … unless the relevant conduct constitutes reckless or willful misconduct, gross negligence, or an intentional tort under any applicable State law"; and
- no liability, also, for a "determination not to provide access to an eligible investigational drug."[60]

Discussion of Selected Provisions in the Right to Try Act

Eligible Patients

The Right to Try Act defines eligibility, in part, as a person diagnosed with a "life threatening disease or condition." That definition differs from many of the state-passed laws, as well as from what FDA preferred: that the definition make clear patients were eligible only if they faced a "terminal illness."[61] FDA Commissioner Gottlieb noted that "[many] chronic conditions are life-threatening, but medical and behavioral interventions make them manageable."[62] Examples of such diseases or conditions are diabetes and heart disease.

Speaking in support of right to try bills, supporters told of people facing death who, with no alternatives remaining, would be willing to risk an experimental drug that might even hasten their death.[63] By not limiting eligibility to those at the end of options, the Right to Try Act could allow people with chronic conditions to take extreme risks rather than live a normal lifespan with treatments now available. Because of the broad eligibility, manufacturers could see a significant

[57] FFDCA §561B(c) [21 U.S.C. §360bbb-0a(c)].

[58] FFDCA §561B(d)(1) [21 U.S.C. §360bbb-0a(d)(1)].

[59] FFDCA §561B(d)(2) [21 U.S.C. §360bbb-0a(d)(2)].

[60] P.L. 115-176, §2(b).

[61] Statement of Scott Gottlieb, M.D., Commissioner of Food and Drugs, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, October 3, 2017, https://www.fda.gov/NewsEvents/Testimony/ucm578634.htm.

[62] Statement of Scott Gottlieb, M.D., Commissioner of Food and Drugs, before the Subcommittee on Health, Committee on Energy and Commerce, U.S. House of Representatives, October 3, 2017, https://www.fda.gov/NewsEvents/Testimony/ucm578634.htm.

[63] For example, Rep. Barton during House floor debate on S. 204, Congressional Record, May 22, 2018, p. H4359, https://www.congress.gov/crec/2018/05/22/CREC-2018-05-22-pt1-PgH4355.pdf.

increase in requests. If Congress revisits the Right to Try Act, Members might consider the definition and clarify what they want for patients and manufacturers.

Informed Consent

The Right to Try Act makes it mandatory that before eligible patients receive an investigational drug, they give the treating doctor their informed consent in writing—but it does not define "informed consent."[64] Other right to try bills, including the House-passed H.R. 5247 (115th Congress), included more specific direction for consent, such as criteria already laid out in 21 CFR Part 50.[65] The Right to Try Act neither provides nor requires the development of such criteria. It thus may weaken patient protections that FDA's expanded access program provides. The Right to Try Act also eliminates the requirement that an IRB review the investigational use of a drug.[66]

If Congress decides to revisit the Right to Try Act, it may seek to create a more explicit informed consent requirement and some outside oversight to reduce the risk to patients either by well-meaning but less knowledgeable physicians or by unscrupulous actors some opponents of the law anticipate.[67]

Data to FDA

Clinical Outcomes

It sometimes takes thousands of patients to establish an accurate evaluation of a drug's safety and effectiveness. Researchers exclude from the clinical trial patients who—for reasons other than the drug's effectiveness—may not show evident benefit from the drug. Those are the patients who would get access through the Right to Try Act pathway.

The Right to Try Act prohibits FDA from using clinical outcome data related to use under this section "to delay or adversely affect the review or approval of such drug."[68] This might make a sponsor more likely to approve the use of its investigational drug under this pathway. The Right to Try Act, however, includes two exceptions. It allows FDA to use those data if the agency determines their use is "critical to determining [the drug's] safety" or if the sponsor requests use of such outcomes.[69] If drug sponsors find that this remains an obstacle to their permitting access to investigational drugs, Congress could work with them, FDA, and patient advocacy groups to devise another approach.

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[64] FFDCA §561B(a)(1)(C) [21 U.S.C. §360bbb-0a(a)(1)(C)].

[65] 21 C.F.R. 312.305(c)(4); Rep. Walden, during House debate on S. 204, May 22, 2018, pp. H4357-4358, https://www.congress.gov/crec/2018/05/22/CREC-2018-05-22-pt1-PgH4355.pdf; and Letter to Speaker Ryan and Minority Leader Pelosi, dated May 21, 2018, from 104 advocacy groups, including the American Cancer Society Cancer Action Network, the American Lung Association, the Cystic Fibrosis Foundation, and the Leukemia & Lymphoma Society, as entered into the record by Rep. Castor during House debate on S. 204, May 22, 2018, p. H4358, https://www.congress.gov/crec/2018/05/22/CREC-2018-05-22-pt1-PgH4355.pdf.

[66] FFDCA §561B(b) [21 U.S.C. §360bbb-0a(b)].

[67] Rep. Pallone, during House floor debate on S. 204, Congressional Record, May 22, 2018, p. H4360, https://www.congress.gov/crec/2018/05/22/CREC-2018-05-22-pt1-PgH4355.pdf.

[68] FFDCA §561B(c)(1) [21 U.S.C. §360bbb-0a(c)(1)].

[69] FFDCA §561B(c)(1)(A) & (B) [21 U.S.C. §360bbb-0a(c)(1)(A)&(B)].

Adverse Events

The Right to Try Act requires the manufacturer to report once a year to FDA, including an account of all serious adverse events that occurred in the preceding 12 months.[70] It does not require immediate reporting of adverse events.[71] This is less than what FDA requires of sponsors of approved drugs and investigational drugs provided in clinical trials or under expanded access. All must periodically inform FDA of such events—and immediately if the event is "serious and unexpected."[72] An adverse event may not be clearly attributable to a drug. A clustering of such reports, though, could signal FDA that this might be something worth exploring.

If Congress were to reconsider the Right to Try Act, it could explore with stakeholders—FDA, drug sponsors, and physicians and patients who use this pathway—ways to make data available to advance the goal of developing safe and effective drugs while protecting the legitimate business interests of manufacturers and the access of seriously ill individuals to try risky drugs.

Disclosure

The Right to Try Act requires the manufacturer or sponsor to submit an annual summary to FDA to include "the number of doses supplied, the number of patients treated, the uses for which the drug was made available, and any known serious adverse events."[73] FDA has issued a proposed rule to implement this annual reporting requirement, which will not become effective until FDA promulgates a final rule and establishes a deadline for such reports.[74] The Right to Try Act also requires FDA to post an annual summary on its website to include the number of drugs for which (1) the agency has determined the need to use clinical outcomes in the review or approval of an investigational drug, (2) the sponsor requested that clinical outcomes be used, and (3) the clinical outcomes were not used.[75]

Congress may choose to revisit these reporting requirements, to require the manufacturer or sponsor to provide more information to FDA, to require FDA to make public additional information, or both.

Financial Cost to Patient

FDA's expanded use process permits a sponsor to charge a patient for the investigational drug, but only to recover the direct costs of making the drug available, as defined under 21 C.F.R. 312.8(d).[76] This includes costs to manufacture the drug in the quantity needed or costs to acquire the drug from another source (e.g., shipping, handling, storage).[77] The sponsor cannot charge for development costs or to make a profit. The Right to Try Act extends this requirement to drugs that

[70] FFDCA §561B(d)(1) [21 U.S.C. §360bbb-0a(d)(1)].

[71] Letter to Speaker Ryan and Minority Leader Pelosi, dated May 21, 2018, from 104 advocacy groups, including the American Cancer Society Cancer Action Network, the American Lung Association, the Cystic Fibrosis Foundation, and the Leukemia & Lymphoma Society, as entered into the record by Rep. Castor during House debate on S. 204, May 22, 2018, p. H4358, https://www.congress.gov/crec/2018/05/22/CREC-2018-05-22-pt1-PgH4355.pdf.

[72] 21 C.F.R. §314.80(c)(1)(i), 21 C.F.R. §312.32(c)(1).

[73] FFDCA §561B(d)(1) [21 U.S.C. §360bbb-0a(d)(1)].

[74] FDA, "Annual Summary Reporting Requirements Under the Right to Try Act," 85 *Federal Register* 44803, July 24, 2020.

[75] FFDCA §561B(d)(2) [21 U.S.C. §360bbb-0a(d)(2)].

[76] 21 C.F.R. §312.8(d)(1).

[77] FDA, "Guidance for Industry: Charging for Investigational Drugs Under an IND—Questions and Answers," p. 6.

sponsors may provide under this pathway.[78] However, it does not require insurers to pay for the drug—or pay for doctor office visits or hospital stays associated with its use or potential adverse outcomes—and these costs may therefore fall on the patient. Congress may consider examining the effect of the Right to Try Act on costs incurred by patients.

Liability Protections

Manufacturers may see liability costs as an obstacle to providing an investigational drug to patients. The no-liability provision in the Right to Try Act seems to remove that obstacle, although it may leave the patient with limited legal recourse. In the past, Congress has sometimes tried to protect both recipients and the manufacturer from harm (e.g., the National Childhood Vaccine Injury Act of 1986 and the Smallpox Emergency Personnel Protection Act of 2003). In those cases, where Congress felt the public health benefit to the larger group outweighed the smaller risk to some, the federal government accepted responsibility for compensating injured patients and indemnifying manufacturers from lawsuits.[79] That has not been the motivating force behind the Right to Try Act. Discussions of earlier versions of liability protections raised concerns that they might not fully protect the manufacturer.[80] As patients use drugs under the Right to Try Act pathway, it is possible that they will test such protections in the courts. This is yet another issue that Congress might pursue.

Concluding Comments

Several questions remain regarding the impact of the Right to Try Act on patients, drug manufacturers, and FDA.

- **First: Will more patients get investigational drugs?** The Right to Try Act requires manufacturers or sponsors to report each year on the number of doses supplied and patients treated as a result of the law, as well as what the drugs were used for and any known serious adverse events.[81] Over time—and perhaps with requesting other data—Congress could determine whether the law has had the effect its sponsors intended.
- **Second: Has the law removed the obstacles to access to investigational drugs?** While the Right to Try Act achieves proponents' objective of removing the FDA application step in a patient's quest for an investigational drug, it does not address other obstacles—such as a limited drug supply or limits on staff and facility resources—that could lead a manufacturer to refuse access to its drugs. Further, it is not clear whether it sufficiently deals with the obstacles it does address—use of clinical outcomes data and liability protection. While the reporting required by the Right to Try Act was not designed to answer those questions, Congress could ask GAO to evaluate the law's impact on manufacturers' willingness to provide investigational drugs under this pathway.

[78] FFDCA §561B(b) [21 U.S.C. §360bbb-0a(b)].

[79] The National Childhood Vaccine Injury Act of 1986 (P.L. 99-660) established the National Vaccine Injury Compensation Program. The Smallpox Emergency Personnel Protection Act of 2003 (P.L. 108-20) established the Smallpox Vaccine Injury Compensation Program.

[80] Bexis, "Federal Right to Try Legislation—Is It Any Better?" Drug & Device Law, September 5, 2017, https://www.druganddevicelawblog.com/2017/09/federal-right-to-try-legislation.

[81] FFDCA §561B(d)(1) [21 U.S.C. §360bbb-0a(d)(1)].

- **Third: How will this affect FDA?** One news article referred to the Right to Try Act's "bizarre twist," as FDA must determine its role in implementing a law whose function is to remove FDA from the situation.[82] Writing in opposition to the bill, four former FDA commissioners warned that it would "create a dangerous precedent that would erode protections for vulnerable patients."[83] That is something Congress may choose to address.

The Right to Try Act concludes with a "Sense of the Senate" section that appears to acknowledge that this legislation offers minimal opportunity to patients. It is explicit in asserting that the new law "will not, and cannot, create a cure or effective therapy where none exists." The legislation, it says, "only expands the scope of individual liberty and agency among patients." The drafters realistically end that phrase with "in limited circumstances."

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Susan Thaul, retired CRS Specialist in Drug Safety and Effectiveness, was the author of a previous version of this report.

Disclaimer

[82] For almost a decade, the Goldwater Institute has been working toward the goal it achieved with the signing of the Right to Try Act. It says that "people have a fundamental right to try to save their own lives without applying to the federal government for permission." (Goldwater Institute quoted in Erin Mershon, "Drug makers have to post policies for patients seeking experimental medicines. Not all do." Stat+, April 5, 2018, https://www.statnews.com/2018/04/05/drug-makers-compassionate-use-policies/.)

[83] Laurie McGinley, "Former FDA commissioners say right-to-try bills could endanger 'vulnerable patients,'" *Washington Post*, March 18, 2018, https://www.washingtonpost.com/news/to-your-health/wp/2018/03/18/former-fda-commissioners-say-right-to-try-bills-could-endanger-vulnerable-patients/?utm_term=.3fe265fa04eb.

United States Government Accountability Office

Report to Congressional Committees

September 2019

INVESTIGATIONAL DRUGS

FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients

GAO Highlights

Highlights of GAO-19-630, a report to congressional committees

September 2019

INVESTIGATIONAL DRUGS

FDA and Drug Manufacturers Have Ongoing Efforts to Facilitate Access for Some Patients

Why GAO Did This Study

When investigational drugs show promise for treating serious or life-threatening diseases, patients are often interested in obtaining access to them. Congress included a provision in the FDA Reauthorization Act of 2017 for GAO to review actions taken to facilitate access to these drugs.

This report describes (1) actions FDA and drug manufacturers have taken to broaden eligibility criteria for clinical trials, (2) actions FDA has taken to facilitate access to investigational drugs outside of clinical trials, and (3) information drug manufacturers have communicated to patients and physicians about access to investigational drugs outside of clinical trials.

GAO reviewed laws, regulations, FDA documents, and manufacturer policies and interviewed FDA officials and a non-generalizable selection of 10 manufacturers and 14 other stakeholders (including patient advocacy and physician organizations). The manufacturers were developing drugs to treat serious or life-threatening diseases, and were selected for variation in company size. GAO also reviewed information that a non-generalizable selection of 29 manufacturers communicated through their websites about access to investigational drugs outside of clinical trials. GAO selected manufacturers for variation in the type of serious diseases their investigational drugs were intended to treat, company size, and other factors.

HHS provided technical comments on a draft of this report, which GAO incorporated as appropriate.

View GAO-19-630. For more information, contact John E. Dicken at (202) 512-7114 or dickenj@gao.gov.

What GAO Found

Individuals may access investigational drugs—those not yet approved for marketing in the United States by the Food and Drug Administration (FDA)—by participating in clinical trials conducted by drug manufacturers to test drug effectiveness and safety. FDA has ongoing efforts to help manufacturers identify the circumstances under which they could broaden clinical trial eligibility criteria to include patients who are commonly excluded, such as pediatric patients and patients with impaired liver and kidney function, without compromising study results.

- FDA issued guidance in March 2019 with recommendations on ways manufacturers could broaden eligibility criteria for cancer clinical trials, when clinically appropriate. In June 2019, FDA issued related guidance that applies to a wider range of clinical trials beyond cancer trials.
- One of the 10 manufacturers GAO interviewed reported broadening its eligibility criteria to include more patients, such as those with HIV. Another manufacturer has begun reviewing its eligibility criteria and expects to include adolescents, as appropriate, in future studies—a population that has generally been excluded from trials. However, these and two other manufacturers cited challenges in these efforts. One stated that expanding participation to patients who use other medications, for example, could adversely affect a study's ability to identify the effects of the studied drug.

Outside of clinical trials, patients with certain medical conditions, who are unable to enroll in a clinical trial, and have no other comparable medical options, may request to obtain access to investigational drugs. This can occur under FDA's expanded access program, or through a 2018 federal law known as "Right to Try." Under either pathway, a patient can only access the investigational drug if its manufacturer agrees to the request. FDA has taken steps to facilitate access to investigational drugs outside of clinical trials, and most manufacturers in GAO's review communicated information to patients and physicians through their websites about how to access their investigational drugs outside of clinical trials. For example:

- Since 2017, FDA took steps to simplify its expanded access program to make it easier to participate. In addition, to address concerns raised by manufacturers, FDA clarified guidance on how it would review data resulting from the program. Seven of the 10 manufacturers GAO interviewed viewed the guidance as an improvement.
- GAO's review of information communicated by 29 manufacturers on their websites found that 23 had policies about accessing investigational drugs outside of clinical trials. At the time of GAO's review, 19 of the 23 stated they would consider individual requests for access, while the other four stated they would not. More than half of the manufacturers stated that if they approve a request, they require additional steps, such as FDA review of the request.

Contents

Abbreviations

Federal RTT Act	federal Right to Try Act
FDA	Food and Drug Administration
FDARA	Food and Drug Administration Reauthorization Act of 2017
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IND	investigational new drug application
IRB	institutional review board

GAO U.S. GOVERNMENT ACCOUNTABILITY OFFICE
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September 9, 2019

The Honorable Lamar Alexander
Chairman
The Honorable Patty Murray
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Frank Pallone, Jr.
Chairman
The Honorable Greg Walden
Republican Leader
Committee on Energy and Commerce
House of Representatives

Before drugs or biologics are approved for marketing in the United States by the Food and Drug Administration (FDA), they are considered investigational.[1] As part of the drug development process, these investigational drugs are tested for safety and effectiveness on humans in clinical trials. When investigational drugs show promise for treating serious or life-threatening diseases or conditions such as metastatic cancer, patients and physicians are often interested in obtaining access to them before they are approved.[2] While some patients may obtain access to these drugs by participating in clinical trials, not all patients are able to participate—for example, because they do not meet the eligibility criteria that manufacturers have established for enrolling in a study.[3]

[1]See 21 C.F.R. § 312.3 (2018). Drugs are defined to include, among other things, articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease, and include components of those articles. See 21 U.S.C. §§ 321(g)(1)(B),(D). Biologic products (referred to as biologics in this report) are materials, such as viruses, therapeutic sera, toxins, antitoxins, vaccines, or analogous products to prevent, treat, or cure human diseases or injuries. See 21 C.F.R. § 600.3(h) (2018). In general, biologics are derived from living sources, such as humans, animals, and microorganisms. For the purpose of this report, we refer to drugs and biologics collectively as "drugs."

[2]A disease is characterized by specific signs and symptoms (e.g., Alzheimer's disease) whereas a condition is an unhealthy state (e.g., chronic pain).

[3]Eligibility criteria define the patient population to be studied in a clinical trial. Inclusion criteria specify the characteristics required for participation, such as the stage of a disease. Exclusion criteria specify the characteristics that disqualify patients from participation, such as the presence of comorbidities or being too young or too old.

Questions have been raised in recent years about whether clinical trial eligibility criteria are too narrow and exclude patients who are likely to be treated once a drug is approved, and FDA has historically provided guidance to manufacturers to help them consider the circumstances under which they could broaden these criteria without compromising study results or raising ethical issues.[4]

Outside of clinical trials, patients who are unable to participate in the trials, and who have certain medical conditions, such as life-threatening conditions, and no comparable medical options, can seek access to investigational drugs through two pathways: 1) FDA's expanded access program and 2) the federal Right to Try Act (federal RTT Act).[5] Under either of these two pathways, access to the investigational drug can only occur if the drug manufacturer agrees to provide access.

Requests to obtain access to investigational drugs through FDA's expanded access program must be reviewed by both FDA and an institutional review board (IRB) in addition to being agreed upon by the drug manufacturer.[6] Some stakeholders—including physician and patient advocacy groups—have criticized FDA's program for being too complex and burdensome to entities involved, which they contend could pose a barrier to individual patients' access to these drugs. However, others argue that FDA is not a barrier because it allows most requests for expanded access to proceed and because factors beyond FDA's program—such as a manufacturer's approval—prevent patients from

[4]For example, FDA has issued guidance documents with recommendations to include patient populations in clinical trials that have been typically excluded from participation, such as elderly patients and pregnant women. See Food and Drug Administration, *Guideline for the Study of Drugs Likely to be Used in the Elderly* (Rockville, Md.: November 1989) and *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials Draft Guidance for Industry* (Silver Spring, Md.: April 2018).

[5]See Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, § 402, 111 Stat. 2296, 2365 (authorizing expanded access) (codified as amended at 21 U.S.C. § 360bbb); Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, Pub. L. No. 115-176, 132 Stat. 1372 (2018) (codified at 21 U.S.C. § 360bbb-0a).

[6]FDA determines whether to allow expanded access requests to proceed, after which an IRB must approve patients' expanded access treatment plans.

An IRB is any board, committee, or other group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects. The primary responsibility of an IRB is to ensure protections for human volunteers in clinical trials and that informed consent will be obtained.

obtaining access. In 2017, we found that FDA allowed 99 percent of the requests under its expanded access program to proceed. We also found that the agency and other stakeholders had taken steps to simplify and improve the expanded access process.[7] For example, FDA shortened the form required for individual patient requests, and it partnered with the Reagan-Udall Foundation to develop a website—referred to as the Expanded Access Navigator—to help physicians and patients locate drug manufacturers' expanded access policies.[8]

The other pathway for obtaining investigational drugs outside of clinical trials—the federal RTT Act—was established by law in May 2018. This provided another pathway for individuals with life-threatening diseases or conditions to seek access to investigational drugs without a requirement for FDA or IRB involvement.[9] Some stakeholders, including some physicians and medical ethicists, have questioned whether patient safety could be compromised by allowing access to investigational drugs without FDA and IRB review and whether the new pathway will improve access for patients because it does not compel manufacturers to allow access to their investigational drugs.

[7]GAO, *Investigational New Drugs: FDA Has Taken Steps to Improve the Expanded Access Program but Should Further Clarify How Adverse Events Data Are Used*, GAO-17-564 (Washington, D.C.: July 11, 2017).

[8]The Reagan-Udall Foundation is a non-profit organization that was established by Congress to assist FDA. See 21 U.S.C. § 379dd. The Expanded Access Navigator was launched in July 2017. See Reagan-Udall Foundation, *Expanded Access Navigator*, accessed May 28, 2019, http://navigator.reaganudall.org/. This website complemented a provision in the 21st Century Cures Act that required certain manufacturers to make their expanded access policies publicly available. Pub. L. No. 114-255, § 3032, 130 Stat. 1033, 1100 (2016) (codified as amended at 21 U.S.C. § 360bbb-0). Under this requirement, as amended by the FDA Reauthorization Act of 2017, manufacturers must make their policies publicly available, such as by posting them on a publicly available internet website, beginning on the earlier of (a) the initiation of a phase II or phase III study for a drug or (b) as applicable, 15 days after the drug receives a designation as a breakthrough therapy, fast track product, or regenerative advanced therapy. 21 U.S.C. § 360bbb-0(f) (as amended by Pub. L. No. 115-52, § 610(c), 131 Stat. 1005, 1053).

[9]A number of states have enacted related legislation, referred to as Right-to-Try laws, placing limitations under state law on liability and licensing actions against individuals or entities involved in the care of individuals seeking access to drugs that have successfully completed phase I clinical trials and met other conditions. By May 2018, 40 states had enacted such laws. See National Conference of State Legislatures, *"Right to Try" Experimental Prescription Medicines State Laws and Legislation for 2014–2018,* accessed June 13, 2019, http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx#Right_to_Try.

The FDA Reauthorization Act of 2017 (FDARA) included a provision for us to describe actions taken by FDA and drug manufacturers to facilitate individual access to investigational drugs.[10] This report examines

1. actions FDA and drug manufacturers have taken to broaden patient eligibility criteria for clinical trials,
2. actions FDA has taken to help facilitate access to investigational drugs outside of clinical trials, and
3. information drug manufacturers have communicated to patients and physicians about access to their investigational drugs outside of clinical trials.

To describe what actions FDA and drug manufacturers have taken to broaden patient eligibility criteria for clinical trials, we reviewed FDA guidance, reports and other related documents and interviewed knowledgeable FDA officials about the agency's ongoing or planned actions on this topic. We also analyzed information collected through interviews with, or written responses to, questions from a non-generalizable selection of 10 drug manufacturers about any ongoing or planned actions they had to broaden the eligibility criteria for their clinical trials, challenges associated with broader criteria, and other efforts to increase participation in clinical trials. We selected the drug manufacturers to achieve variation in company size and because they were developing drugs or biologics to treat serious or life-threatening diseases or conditions.

To describe what actions FDA has taken to help facilitate access to investigational drugs outside of clinical trials, we reviewed laws, FDA regulations and guidance, and FDA's website and other related documents about FDA's expanded access program and the federal RTT pathway. We also interviewed knowledgeable FDA officials about the agency's ongoing and planned actions related to this topic and a non-generalizable selection of 24 stakeholder organizations to obtain their views on FDA's actions. The organizations included the 10 selected manufacturers noted above; three trade groups representing manufacturers; three patient advocacy organizations; two physician organizations; two public policy research organizations; two organizations that work with manufacturers to facilitate access outside of clinical trials;

[10]Pub. L. No. 115-52, § 610(a)(2), 131 Stat. 1052.

one organization focused on improving access to investigational drugs through clinical trials; and one physician representing a research organization. We selected patient advocacy and physician organizations that broadly represented the views of patients and physicians, including those stating they have experience in seeking access to investigational drugs outside of clinical trials. In addition, we selected organizations to provide a range of perspectives regarding FDA's expanded access program and the federal RTT pathway.

To describe what information drug manufacturers have communicated to patients and physicians about access to their investigational drugs outside of clinical trials, we reviewed the websites of a non-generalizable selection of 29 drug manufacturers.[11] We first selected 21 drug manufacturers that were developing investigational drugs or biologics intended to treat 10 serious diseases to achieve variation across several factors.[12] These factors included company size, participation in the Expanded Access Navigator, and whether the manufacturer had an investigational drug or biologic that FDA designated as a breakthrough therapy, fast track product, or regenerative medicine advanced therapy in fiscal year 2018.[13] Two of these 21 manufacturers were among the 10 we interviewed. In addition, we reviewed the websites of the other eight drug manufacturers we interviewed. We conducted our review of manufacturer websites between January 31, 2019, and March 12, 2019, by using a data collection instrument that included a standard set of questions for collecting information on the availability of information, procedures for making a request for access to investigational drugs, and the factors that the manufacturer would consider in evaluating requests. For manufacturers that we determined had not communicated information on

[11]Manufacturers are required to make such information "public and readily available, such as by posting such policies on a publicly available Internet website." 21 U.S.C. § 360bbb-0(b).

[12]We selected the following 10 serious diseases: Duchenne muscular dystrophy, Alzheimer's disease, pancreatic cancer, metastatic breast cancer, acute myeloid leukemia, human immunodeficiency virus (HIV) infection, schizophrenia, cystic fibrosis, hemophilia type a or b, and chronic heart failure. We selected these 10 diseases because they are generally recognized as serious and reflect a range of types of diseases (e.g., neurological, viral, psychiatric, cancer).

[13]Manufacturers voluntarily participate in the Expanded Access Navigator by providing links to their expanded access policies posted on their websites. Breakthrough therapy, fast track product, and regenerative medicine advanced therapy designations are used by FDA to expedite the development and review of certain drugs and biologics intended to treat conditions that are generally considered serious.

their websites about access to investigational drugs at the time of our review, we contacted them to verify this. To supplement our analysis, we reviewed additional information that manufacturers communicated on their websites, such as whether they provided information about access to specific investigational drugs.

We conducted this performance audit from August 2018 to September 2019 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

Clinical Trials

When patients are seeking access to investigational drugs, their first option is to consider whether they can obtain them through participation in a clinical trial. Clinical trials are a step in the drug development process through which a drug manufacturer assesses the safety and effectiveness of its investigational drug through human testing. A clinical trial can take place in a variety of settings (e.g., research hospitals, universities, and community clinics) and geographic locations, and is led by a principal investigator that is typically a physician.

Manufacturers establish clinical trial eligibility criteria to define the patient population to be studied, and only patients who meet those criteria can participate. These criteria can vary depending on the drug being studied and its intended use. Patient eligibility criteria consist of both inclusion and exclusion criteria. Inclusion criteria specify the characteristics of the patient that are required for participation, such as the stage or characteristics of a disease, and typically identify a patient population in which it is expected that the manufacturer can demonstrate the effect of an investigational drug. In comparison, exclusion criteria specify the characteristics that disqualify patients from clinical trial participation and can include factors that could mask the effect of an investigational drug, such as the presence of comorbidities or simultaneous use of other

drugs.[14] Certain patient populations, such as children and pregnant women, may also be excluded from clinical trial participation because of ethical reasons.[15]

Drug manufacturers, FDA, and IRBs each have responsibilities as part of the clinical trial process. In order to test an investigational drug on human volunteers in clinical trials, a manufacturer must first submit an investigational new drug application (IND) to FDA. FDA is responsible for reviewing the IND, which includes various components such as the clinical trial protocol that describes the patient eligibility criteria, the medications and dosages to be studied, and other details. In turn, an IRB is responsible for reviewing and approving the clinical trial protocol as well as reviewing the informed consent form for the study.[16] In general, clinical trials that involve human volunteers can begin after FDA has reviewed and allowed the IND to proceed and the IRB has given its approval.

An investigational drug typically goes through three phases of clinical trials before an application is submitted to FDA for marketing approval.[17] At any point during the clinical trials, FDA could issue a clinical hold on the existing IND that would delay the proposed clinical trials or suspend the ongoing clinical trials. When a proposed or ongoing study is placed on a complete clinical hold, the investigational drug cannot be administered

[14]A comorbidity is a medical condition beyond the condition an investigational drug is intended to treat.

[15]For example, pregnant women have been excluded because of concerns about the potential for injury to the fetus.

[16]Many institutions (such as research hospitals) have their own IRB to oversee human subjects research conducted within the institution or by the staff of the institution—these are commonly referred to as local IRBs. A physician who does not have access to a local IRB typically uses an independent IRB, which is not associated with any institution.

[17]According to FDA officials, in some cases when a new drug is being tested for a life-threatening condition, the drug development process may be expedited by going through only one or two phases of clinical trials before an application is submitted to FDA for marketing approval. In addition, postmarket studies are required for some drugs that FDA has approved for marketing.

to any human volunteers.[18] Traditionally, the three clinical trial phases are the following:

- **Phase I:** This clinical trial phase generally tests the safety of the drug on about 20 to 80 healthy volunteers. The goal of this phase is to determine the drug's most frequent side effects and how it is metabolized and excreted. If the drug does not show unacceptable toxicity in the phase I clinical trials, it may move on to phase II.
- **Phase II:** This clinical trial phase assesses the drug's safety and effectiveness on people who have a certain disease or condition, and typically the assessment is conducted on a few dozen to hundreds of volunteers. Generally, during this phase some volunteers receive the drug and others receive a control, such as a placebo. If there is evidence that the drug is effective in the phase II clinical trials, it may move on to phase III.
- **Phase III:** This clinical trial phase generally involves several hundreds to thousands of volunteers who have a certain disease or condition and gathers more information about the drug's safety and effectiveness, again while being compared to a control.

If phase III clinical trials are successfully completed, the drug may move on to FDA's review and approval process. When seeking FDA's approval to market a drug in the United States, the manufacturer submits an application to FDA that includes the data from the safety and efficacy clinical trials for FDA to review.[19] Safety data include clinical trial results about a drug's toxicity (e.g., the highest tolerable dose) and adverse events that may result from exposure to the drug. Efficacy data include information on whether the drug demonstrated a health benefit over a

[18]See 21 C.F.R. § 312.42 (2018). A clinical hold may be either a complete clinical hold or a partial clinical hold. Reasons for imposing complete clinical holds can include human volunteers being subject to unreasonable and significant risks of illness or injury from the drug. According to FDA officials, the agency may also place a drug on a partial clinical hold during which the drug cannot be administered to certain types of patients. See Food and Drug Administration, *Guidance for Industry: Submitting and Reviewing Complete Responses to Clinical Holds* (Rockville, Md.: October 2000).

[19]When seeking approval for marketing of a new drug in the United States, the manufacturer submits to FDA a new drug application. See 21 C.F.R. § 314.50 (2018). When seeking approval for marketing of a new biologic in the United States, the manufacturer submits to FDA a biologics license application. See 21 C.F.R. § 601.2 (2018).

placebo. FDA reviews the information in the application to either approve or not approve the drug.

FDA's Expanded Access Program

If a patient seeking access to an investigational drug is not able to participate in the drug's clinical trial (e.g., because of the study's eligibility criteria or geographic location), another pathway to potentially obtain access to the drug outside of a clinical trial is through FDA's expanded access program. Under the program, a licensed physician can submit a request for access to an investigational drug for treatment use on behalf of a patient and may do so during or after phase I, II, or III of clinical trials. To allow access to an investigational drug under the program, FDA must determine that a patient has a serious or immediately life-threatening disease or condition and has no other comparable medical options, among other criteria.[20]

FDA's goals for the program are to facilitate the availability of investigational drugs when appropriate, ensure patient safety, and preserve the clinical trial development process.[21] FDA is responsible for determining whether to allow individual requests to proceed to treatment once the manufacturer has agreed to provide access.[22] If FDA allows the request to proceed, an IRB must approve the clinical treatment plan that is submitted as part of the individual request and review the informed consent form.[23] The licensed physician treating a patient under expanded access would be required to report to FDA any unexpected serious adverse reactions that occur during treatment for which there is a reasonable possibility that the drug caused the reaction.[24]

[20]See 21 C.F.R. § 312.305(a) (2018).

[21]FDA's expanded access program includes options through which requests can be submitted for individual patients or for groups of patients. This report focuses on individual patient requests. For more information about the broader expanded access program, see GAO-17-564.

[22]For individual requests, physicians can submit FDA Form 3926 (the Individual Patient Expanded Access Investigational New Drug Application) or FDA Form 1571 (the Investigational New Drug Application).

[23]See 21 C.F.R. § 312.305(c)(4) (2018).

[24]See 21 C.F.R. § 312.32(c) (2018).

The Federal RTT Act

In 2018 the federal RTT Act established another pathway through which patients may potentially obtain access to investigational drugs outside of clinical trials. To be eligible under the law, a patient must have been diagnosed with a life-threatening disease or condition, have exhausted approved treatment options, and be unable to participate in a clinical trial involving the investigational drug.[25] Obtaining access to investigational drugs through the federal RTT Act primarily requires the involvement of the manufacturer and treating physician. Similar to FDA's expanded access program, treatment can only proceed if the drug manufacturer allows the patient access to its drug. Under the federal RTT Act, the manufacturer is responsible for providing to FDA an annual summary of any use of its drugs under this pathway that includes information on any known serious adverse events.[26] The treating physician is responsible for requesting access to the investigational drug for the patient and for obtaining written informed consent from or on behalf of the patient if the manufacturer agrees to provide access. Eligibility of an investigational drug for patient use through this pathway is based on certain criteria, including that the drug has completed phase I clinical trials, the manufacturer has not discontinued clinical development of the drug, and the drug has not been placed on a clinical hold.[27] Unlike FDA's expanded access program, the federal RTT Act does not require the FDA or an IRB to review individual requests for access.

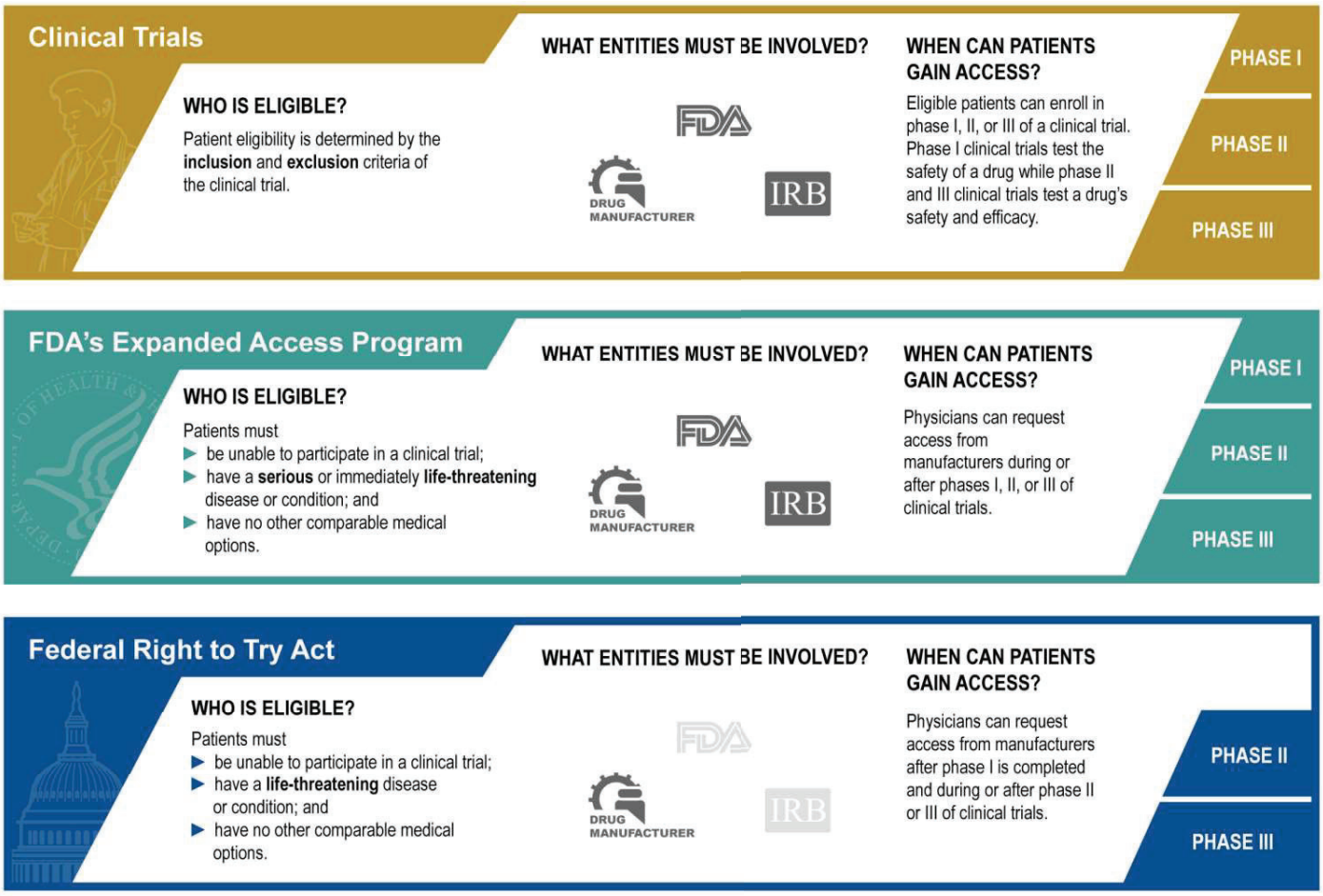
Figure 1 shows a summary of the three pathways through which patients may obtain access to investigational drugs.

[25]Pub. L. No. 115-176, § 2(a), 132 Stat. 1372 (codified in pertinent part to 21 U.S.C. § 360bbb-0a(a)(1)).

[26]FDA is also responsible for posting an annual summary report on the use of investigational drugs through the RTT pathway on its website.

[27]See Pub. L. No. 115-176, § 2(a),132 Stat. 1372 (codified in pertinent part to 21 U.S.C. § 360bbb-0a(a)(2)).

Figure 1: Access to Investigational Drugs through Three Pathways



FDA = Food and Drug Administration. IRB = institutional review board.
Source: GAO analysis of FDA information. | GAO-19-630

FDA Issued Guidance to Help Manufacturers Broaden Clinical Trial Eligibility Criteria and Two Manufacturers We Interviewed Took Steps to Broaden Their Criteria

Some patients, such as those with compromised liver and kidney function, have traditionally been excluded from clinical trials. FDA has ongoing efforts to help drug manufacturers identify the circumstances under which they could broaden their eligibility criteria to include such patients without compromising study results. These efforts include issuing recent guidance with recommendations for including certain patients in clinical trials for cancer drugs. Officials from one of the 10 drug manufacturers we interviewed told us they had broadened their eligibility criteria and another one was taking steps to do so, but these officials and others noted challenges to broadening eligibility criteria.

FDA public workshop on broadening eligibility criteria. In April 2018, FDA held a public workshop with stakeholders—including drug manufacturers, patient advocacy groups, and government agencies—to discuss ways drug manufacturers and other investigators could safely broaden eligibility criteria for clinical trials and to inform FDA guidance on this topic. In July 2018 FDA publicly released a report summarizing the workshop, in accordance with FDARA.[28] According to the report, stakeholders at the meeting emphasized the importance of broadening clinical trial eligibility, when appropriate, to include more patients who will likely use the drug if it is approved. Stakeholders recommended that investigators ensure that the eligibility criteria for each of their clinical trials are scientifically justifiable, rather than, for example, “copying and pasting” a narrow set of criteria from a prior study without considering if the exclusions are valid for scientific reasons. According to the report, this practice can unnecessarily limit eligibility for certain patients. While stakeholders commented that assessing whether eligibility criteria are scientifically justifiable may require additional time and resources, they emphasized it could lead to the removal of unnecessarily restrictive eligibility criteria and thereby increase participation among patient populations that have been typically excluded from clinical trials, such as pediatric patients and patients with compromised liver and kidney function.

[28]FDARA required that FDA, in coordination with other stakeholders, convene a public meeting to discuss clinical trial inclusion and exclusion criteria and make a report on the topics discussed at the meeting available on FDA’s website. See Pub. L. No. 115-52, § 610(a)(1), 131 Stat. 1051 (codified at 21 U.S.C. § 360bbb note).

See Food and Drug Administration, *Public Workshop: Evaluating Inclusion and Exclusion Criteria in Clinical Trials* (Silver Spring, Md.: August 2018).

FDA guidance on eligibility criteria. In March 2019, FDA issued four new draft guidance documents and finalized one guidance document with recommendations for drug manufacturers to broaden clinical trial eligibility criteria for drugs that treat cancer. The guidance recommends that manufacturers include certain patient populations that have typically been excluded from participation.[29] The patient populations are adolescents; pediatrics (children and adolescents); patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections; patients with brain metastases (i.e., cancer that has spread to the brain); and patients with compromised kidney, heart, or liver function, or who have a history of (or concurrent) cancer. According to FDA, the guidance documents are intended to help drug manufacturers and other investigators broaden cancer trial eligibility criteria. This will help improve patient access to investigational drugs and ensure that the results from the clinical trials are generalizable to patients likely to use the drugs once they are approved. In addition, FDA officials have noted that including broader patient populations in clinical trials can lead to new information in a drug's labeling, which will help communicate the safe and effective use of these drugs. Table 1 provides a summary of each of the five guidance documents.

[29]See Food and Drug Administration, *Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials, Guidance for Industry; Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients, Draft Guidance for Industry; Cancer Clinical Trial Eligibility Criteria: Patients with HIV, Hepatitis B Virus, or Hepatitis C Virus Infections, Draft Guidance for Industry*; *Cancer Clinical Trial Eligibility Criteria: Brain Metastases, Draft Guidance for Industry; Cancer Clinical Trial Eligibility Criteria: Patients with Organ Dysfunction or Prior or Concurrent Malignancies, Draft Guidance for Industry* (Silver Spring, Md.: March 2019). FDA's guidance on the inclusion of adolescent patients in cancer clinical trials is final guidance and its guidance on the inclusion of the other four patient populations is draft guidance. Guidance documents represent FDA's current thinking on a topic. Neither draft nor final guidance documents legally bind FDA or confer legal rights on affected individuals. See 21 C.F.R. § 10.115 (2018). According to FDA, this guidance is intended to assist stakeholders who are responsible for the development and oversight of clinical trials.

Table 1: Summary of the Food and Drug Administration's (FDA) Guidance on Including Certain Patients in Cancer Clinical Trials, March 2019

Patient population	Summary
Pediatric patients	FDA recommends that drug manufacturers consider including pediatric patients in adult cancer trials, in part, to prevent delays in the development of and access to potentially effective new cancer drugs for this population. For example, FDA specifies that children aged 2 to 11 should be considered for inclusion. The guidance recommends that they should be considered for inclusion when there is evidence from adult studies demonstrating that children will likely respond to a drug in a way similar to adults, and when there are no concerns about the potential for toxicity related to severe effects on growth and development.
Adolescent patients	FDA recommends that drug manufacturers consider including adolescents aged 12 to 17 in adult cancer clinical trials, in part, because some cancers found in adolescent patients are similar in biology to those found in adults. For example, the guidance recommends that adolescents should be considered for inclusion in early phase cancer clinical trials if they have cancers that have relapsed and after some initial evidence from adult studies is obtained about a drug's toxicity and effect on the body (e.g., how it is absorbed).
Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infections	FDA recommends that drug manufacturers consider including patients with HIV, HBV, and HCV infections in cancer trials, in part, because HIV and HBV infections can be chronically managed, and HCV infections can be cured with certain anti-viral drugs. For example, the guidance recommends that eligibility criteria for patients with cancer and concurrent HIV infection should focus on patients' immune system functioning and use of drugs to treat HIV. To illustrate, the guidance recommends that patients with a history of certain AIDS-defining infections should be eligible if they have not had the infection within the past 12 months.
Patients with cancer spread to the brain	FDA recommends that drug manufacturers consider including patients with cancers that have spread to the brain in cancer trials, in part, because there is an increasing incidence of patients living with cancers that commonly spread to the brain (e.g., breast and lung cancer). For example, the guidance recommends that patients who have active cancer that has spread to the brain be included in cancer trials, as long as the treating physician has determined that the patient does not require immediate treatment for their central nervous system disease.
Patients with compromised organ function	FDA recommends that drug manufacturers consider including patients with compromised kidney, heart, and liver function in cancer trials, in part, because there is an increasing number of such patients given the increasing life expectancy in the general population. For example, the guidance recommends that as data on a drug's toxicity and other effects on the body (e.g., how it is absorbed) become available during drug development, eligibility criteria should be revised to include patients with compromised organ function where safe parameters regarding dosage adjustments have been determined.

Source: GAO summary of FDA documents. | GAO-19-630

Note: FDA's guidance on the inclusion of adolescent patients in cancer clinical trials is final guidance and its guidance for the other patient populations is draft guidance.

In June 2019, FDA issued draft guidance for manufacturers on broadening clinical trial eligibility criteria, in accordance with FDARA.[30] The guidance applies to a wider range of clinical trials beyond cancer trials and includes recommendations to broaden eligibility criteria and considerations for the use of clinical trial designs and other methodologies to help facilitate patient participation.[31] For example, FDA recommends that manufacturers examine each exclusion criterion to determine if it is needed to help assure the safety of trial participants or to achieve the study's objectives. If not, the manufacturer should consider eliminating or modifying the criterion to expand the study population as well as tailoring the exclusion criteria as narrowly as possible to avoid unnecessary restrictions to the study population.

Two manufacturers' efforts to broaden eligibility criteria. Officials from one of the 10 drug manufacturers we interviewed told us they broadened their clinical trial eligibility criteria and another manufacturer we interviewed reported that it was taking steps to do so. These two manufacturers told us they were taking these steps in part because both believe it will facilitate the drug approval process.[32] Officials from one manufacturer stated that they broadened their eligibility criteria by removing exclusions after determining they were not critical to clinical trial designs, including exclusions related to liver function, infections (e.g., HIV), and the use of other medications (e.g., steroids). The officials explained that, since 2015, they have systematically evaluated their eligibility criteria to ensure that they do not unnecessarily exclude patient populations from their clinical trials. Officials from the second manufacturer told us they have begun evaluating whether to remove certain exclusion criteria that they typically use in clinical trials, and added that their efforts are partially in response to FDA's 2018 public workshop report, as described above. For example, the manufacturer is reviewing its exclusion of adolescents in prior clinical trials and officials told us they

[30]See Pub. L. No. 115-52, § 610(a)(3), 131 Stat. 1052 (codified at 21 U.S.C. § 360bbb note). Food and Drug Administration, *Enhancing the Diversity of Clinical Trial Populations—Eligibility Criteria, Enrollment Practices, and Trial Designs, Draft Guidance for Industry* (Silver Spring, Md.: June 2019).

[31]The draft guidance applies to both demographic populations (e.g., sex, race, age) and non-demographic populations (e.g., patients with organ dysfunction, comorbidities).

[32]One manufacturer developing drugs to treat rare diseases stated that because of the small number of patients with such diseases, its eligibility criteria are sufficiently broad in order to recruit a large enough sample for a study.

will likely include adolescents in an upcoming study if they determine that patient safety would not be compromised.

Officials from both manufacturers stated that broader eligibility criteria will allow more patients to access investigational drugs through clinical trial participation. It can also, officials said, help them obtain FDA approval for a drug that extends to a wider range of patients, if the drug is found to be safe and effective. Further, officials from one of the two manufacturers noted that broader eligibility criteria, such as criteria that include patients with infections, could help streamline the process for conducting clinical trials—for example, by eliminating the need to conduct clinical testing to screen for the presence of infections.

Although most drug manufacturers in our review did not report efforts to broaden their eligibility criteria, many noted efforts to address other barriers to clinical trial participation. For example, to address geographic barriers, officials from six of the 10 manufacturers told us they help cover costs for patients to travel to clinical trial sites, such as by reimbursing transportation and hotel costs for patients who travel long distances.[33] In addition, officials from one manufacturer said they completed a pilot clinical trial on diabetes in 2019 that used decentralized trial locations in three states, such as retail health clinics and patients' homes, to help patients overcome challenges with obtaining transportation to trial sites. Similarly, within the next 2 years, another manufacturer is planning to conduct a pilot clinical trial that is fully remote and expects the design to improve patient participation in rural communities.

To address the lack of information about upcoming and ongoing clinical trials that is available to and tailored to patients, two manufacturers launched clinical trial registries in 2015 and 2016, respectively.[34] Officials from one of the manufacturers stated they designed their registry to bridge the gap between the information that patients want about clinical

[33]According to FDA guidance, reimbursement for travel expenses to and from a clinical trial site and associated costs such as airfare and lodging do not raise issues of undue influence on the part of drug manufacturers and are generally considered acceptable practice. See Food and Drug Administration, *Information Sheet, Payment and Reimbursement to Research Subjects, Guidance for Institutional Review Boards and Clinical Investigators, accessed June 18, 2019,* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects.

[34]A clinical trial registry is a web-based search tool that helps patients locate information about ongoing clinical trials, including those conducted by manufacturers.

trials (e.g., information targeted to medical conditions that uses basic terminology), and what is available in ClinicalTrials.gov, a federal database that includes information on privately and publicly funded clinical trial studies.[35] Officials explained that ClinicalTrials.gov is, in general, more targeted to physicians.[36]

In addition, to address barriers associated with the mistrust of research stemming from historical events among African-Americans and other communities, one manufacturer has several ongoing efforts to increase the participation of racially and ethnically diverse populations in its clinical trials.[37] For example, the manufacturer conducts workshops to train minority investigators who conduct clinical trials and requires certain clinical trial sites to be located in areas with minority patient populations of more than 25 percent.

Challenges with broadening eligibility criteria. Officials from four of the 10 drug manufacturers we interviewed—including the two taking steps to broaden their clinical trial eligibility criteria—told us broadening eligibility criteria is challenging. They stated that broader criteria must be carefully balanced with the need to collect evidence from a well-defined population. Officials from one manufacturer explained that removing standard exclusion criteria, such as excluding patients who use other medications, could interfere with the success of their clinical trial if those medications make it difficult to identify the effects of the studied drug. In addition, officials from another manufacturer emphasized that determining whether to remove exclusion criteria takes time and resources because it involves additional study, which could slow down the clinical development of a drug.

[35]In addition to information about clinical trials, ClinicalTrials.gov includes certain information about the availability of expanded access for investigational drugs.

[36]Officials from eight other stakeholders we interviewed similarly commented that ClinicalTrials.gov uses complex terminology, which can be difficult for some patients to understand.

[37]There have been well-documented cases of abuse of African-American participants in clinical research, such as the Tuskegee Syphilis Study.

FDA Took Several Recent Actions to Facilitate Access to Investigational Drugs Outside of Clinical Trials

FDA Simplified the Institutional Review Board Process and Launched a Pilot Program to Facilitate Access to Investigational Drugs Outside of Clinical Trials

To facilitate access to investigational drugs outside of clinical trials, FDA has simplified its expanded access program's IRB review requirements for individual patient requests.[38] FDA made this change in October 2017, in accordance with a provision in FDARA.[39] This provision addressed concerns that FDA's requirement to convene a full IRB to review an expanded access request could result in delays of approvals because full IRBs may not meet regularly. Under the revised process, FDA now allows for a waiver of the requirement for full IRB review when concurrence is obtained by the IRB chair or another designated member. According to FDA officials, the updated process will help reduce the potential burden for physicians, who are responsible for obtaining IRB approval, while still protecting patients.

In addition, to further simplify its expanded access process for individual patient requests, in June 2019 FDA launched a pilot program called Project Facilitate for oncologists and other health care professionals that

[38]See Food and Drug Administration, *Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers, Guidance for Industry* (Silver Spring, Md.: October 2017), 5-6.

Under FDA's expanded access program, a licensed physician can request access to investigational drugs for treatment use on behalf of a patient. FDA must approve the request, and if so, the request must be reviewed by an IRB. Our July 2017 report described actions FDA had taken to simplify the expanded access process, such as issuing a new simplified application form for individual requests and finalizing its related guidance.

FDA's expanded access program includes different processes for requests to access a drug for an individual patient and for requests to access a drug for multiple patients.

[39]Pub. L. No. 115-52, § 610(b), 131 Stat.1053 (codified at 21 U.S.C. § 360bbb note).

treat patients with cancer.[40] According to FDA officials, the pilot program is focused on oncology because the agency receives a large number of individual expanded access requests from oncologists. Under the pilot program, FDA established a new call center that provides a single point of contact where FDA staff are available to answer questions, assist in filling out appropriate paperwork, and facilitate the overall process for requesting and obtaining access to investigational drugs. For example, FDA officials told us that FDA staff may assist oncologists in locating an IRB, if needed. As part of the pilot program, FDA will follow up on individual requests and gather data, such as how many patients received investigational drugs, and if not, why the requests were denied by manufacturers.[41] According to FDA, the agency can use these data to determine how the process is benefiting patients.

Twenty of the stakeholders we interviewed were familiar with FDA's simplified IRB review requirements, and of those, 18 told us these updates were helpful for physicians and patients.[42] For example, officials from one drug manufacturer commented that the new IRB review requirements reduce the amount of time it takes for patients to obtain access to investigational drugs, which is especially important for patients who are very sick. In addition, we spoke to 12 stakeholders about FDA's plans for its pilot program, and of those, nine generally had positive views of the agency's planned activities.[43] Officials from one manufacturer explained that the pilot program could help reduce the burden on oncologists seeking access to investigational drugs for their patients through the expanded access program. On the other hand, the officials from this same manufacturer raised concerns about the potential for FDA to intentionally or unintentionally pressure companies to make their investigational drugs available to patients, should FDA have increased involvement with drug manufacturers as part of the pilot program.

[40]See Food and Drug Administration, *Project Facilitate*, accessed July 10, 2019, https://www.fda.gov/about-fda/oncology-center-excellence/project-facilitate.

[41]FDA officials told us the agency's current plan is to obtain such information from the treating physicians or their health care teams.

[42]Of the 24 stakeholders, four were unfamiliar with the updates to the IRB review requirements.

[43]Of the 24 stakeholders, we spoke to 12 about FDA's plans for its pilot program. We became aware of FDA's plans to conduct the pilot program after we completed many of our stakeholder interviews.

FDA Increased Communication about the Expanded Access Program and the Federal RTT Act to Facilitate Access to Investigational Drugs Outside of Clinical Trials

FDA has also taken recent actions to facilitate access to investigational drugs outside of clinical trials by increasing its communication about the expanded access program and the federal RTT Act.

FDA's increased communication about the expanded access program. In November 2018, FDA updated the web pages for its expanded access program in response to findings from an external assessment that the web pages were difficult to navigate and contained unclear information.[44] FDA created separate web pages for patients, physicians, and drug manufacturers, and tailored information about the expanded access process to each of these stakeholders. In addition, FDA added a new web page with information that is commonly requested by physicians and patients, such as the instructions for completing the form for submitting individual requests and definitions of keywords associated with the expanded access process (e.g., IRB, informed consent).

In addition, in October 2017, in response to a recommendation in our July 2017 report, FDA clarified its guidance for drug manufacturers on how the agency reviews adverse events that occur under FDA's expanded access program.[45] In the 2017 report, we found that some drug manufacturers were concerned that use of adverse event data may influence FDA in making final approval decisions, and that this possibility could contribute to a manufacturer deciding not to grant patients access to their drugs through the expanded access program. In response, we recommended that FDA clearly communicate how the agency will use adverse event data from expanded access use when reviewing drugs and biologics for approval.[46]

[44]See Food and Drug Administration, *Expanded Access*, accessed May 29, 2019, https://www.fda.gov/news-events/public-health-focus/expanded-access.

To identify ways to improve its expanded access program, FDA commissioned an external assessment of the program in 2017 that included obtaining the perspectives of various stakeholders such as health care providers and drug manufacturers. See Food and Drug Administration, *Expanded Access Program Report* (Silver Spring, Md.: May 2018).

[45]See Food and Drug Administration, *Expanded Access to Investigational Drugs for Treatment Use—Questions and Answers, Guidance for Industry* (Silver Spring, Md.: October 2017), 18-19.

[46]See GAO-17-564.

FDA's updated guidance states that FDA is not aware of instances in which adverse event information prevented the agency from approving a drug, and that it is very rare for FDA to place a clinical hold on an investigational drug due to adverse events observed during expanded access treatment.[47] The guidance also explains that several factors make it difficult for FDA to link an adverse event to the expanded use of a drug being considered for approval. For example, the guidance acknowledges that the use of investigational drugs though the expanded access program generally occurs outside of a controlled clinical trial setting and patients receiving such drugs may be sicker than patients participating in a clinical trial, making it more difficult to determine whether the use of the investigational drug has led to the adverse event.

In responding to questions about increased FDA communication about the expanded access program, 19 of the stakeholders we interviewed were familiar with FDA's updated expanded access web pages, and of those, 16 told us they were an improvement.[48] Officials from one physician organization stated that the updated web pages were easier to navigate than the previous web pages and presented information about the process more clearly.

Among the 10 manufacturers we interviewed, we found varying views of FDA's updated guidance on the use of adverse event data.

- Officials from seven of the 10 manufacturers viewed the updated guidance as an improvement. Officials from one of the seven explained that it contributed to their company's decision to allow access to investigational drugs, when appropriate.

[47]For example, see study examining FDA's use of safety information obtained during expanded access to place clinical holds: Jonathan P. Jarow, Steven Lemery, Kevin Bugin, Sean Khozin, and Richard Moscicki, "Expanded Access of Investigational Drugs: The Experience of the Center of Drug Evaluation and Research Over a 10-Year Period," *Therapeutic Innovation & Regulatory Science*, vol. 50, no. 6 (2016). Also see study examining FDA's use of safety information obtained during expanded access to affect labeling: Jonathan P. Jarow and Richard Moscicki, "Impact of Expanded Access on FDA Regulatory Action and Product Labeling," *Therapeutic Innovation & Regulatory Science*, vol. 51, no. 6 (2017).

[48]Of the 24 stakeholders, officials from three stakeholders told us they were unfamiliar with FDA's updated expanded access web pages. We did not ask the other two stakeholders their views on the updated web pages because of the timing of those interviews relative to the timing of FDA's updates.

- Officials from two of the 10 manufacturers did not view the guidance as an improvement. Officials from both manufacturers stated that they still had significant concerns about the potential use of adverse event data by FDA to adversely affect the development of their investigational drugs, such as being used to issue a clinical hold. An official from one of the two manufacturers commented that these concerns remained despite FDA's statement in the guidance that it is difficult for FDA to link expanded access use to a particular adverse event. In addition, officials from two other manufacturers who viewed the guidance as an improvement similarly expressed remaining concerns that adverse events could negatively affect the development of their investigational drugs.
- One manufacturer was unfamiliar with the updated guidance.

Further, officials from four of the 10 drug manufacturers we interviewed, including two who viewed the updated guidance as an improvement, said they believed that manufacturers' concerns about this issue may never be fully resolved even with additional FDA guidance.

In other comments related to FDA's communication on its use of adverse events data from the expanded access program, some drug manufacturers we interviewed noted the merits of using efficacy and safety data from the expanded access program to inform FDA's drug approval decisions. Officials from two of the 10 manufacturers told us they believe that FDA's potential use of adverse event data from expanded access use, but not efficacy data, would be unfair. Officials from one of these two manufacturers cited FDA's updated guidance on adverse events as contributing to their view, referring to FDA's statement that it is unlikely that FDA's program would yield data that is useful to FDA in considering an investigational drug's effectiveness.

However, FDA officials told us that efficacy and safety data from the expanded access program have been used to support drug approvals in several instances. For example, in January 2018 FDA approved the drug Lutathera to treat rare tumors in the pancreas and gastrointestinal tract using efficacy and safety data the manufacturer submitted to FDA from a subset of the roughly 1,200 patients who received the drug through the expanded access program. Officials from four of the 10 manufacturers expressed interest in discussing further with FDA how the agency would evaluate efficacy and safety data from the expanded access program and

use these data to help support a drug's approval and other regulatory decisions.[49]

FDA's communication about the federal RTT Act. In November 2018, FDA launched a new federal RTT web page that outlines both the eligibility requirements for patients interested in seeking access to investigational drugs and the criteria that must be met for an investigational drug to be eligible for use through this pathway.[50] For example, the web page states that patients must be diagnosed with a life-threatening disease or condition to be eligible to access investigational drugs under the federal RTT pathway. Further, the agency plans to issue proposed regulations in September 2019 to implement the federal RTT Act requirement for manufacturers to submit an annual summary to FDA on any use of their investigational drugs under this pathway.[51] The regulations will include a due date for manufacturers to submit the annual summaries as well as information on what they are to contain, according to FDA.

Fourteen of the stakeholders we interviewed were familiar with FDA's new web page on the federal RTT Act, and among those, eight stated that it communicated useful and balanced information for physicians and patients.[52] Officials from the remaining six stakeholders told us they did not find it helpful for physicians or patients. For example, officials from two stakeholders (including one drug manufacturer) commented at the time of our review that the web page could be misleading to some patients if they interpret the federal RTT Act to mean that manufacturers

[49]FDA officials told us they discussed the use of data from the expanded access program to support drug approval decisions at a November 2018 meeting that the Reagan-Udall Foundation sponsored for stakeholders, including drug manufacturers. See Reagan-Udall Foundation for the Food and Drug Administration, *Public Meeting Report: Leveraging Real-World Treatment Experience from Expanded Access Protocols* (Washington, D.C.: November 2018).

[50]See Food and Drug Administration, *Right to Try*, accessed June 19, 2019, https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/right-try.

[51]See Pub. L. No. 115-176, § 2(a), 132 Stat. 1372 (codified in pertinent part at 21 U.S.C. § 360bbb-0a(d)). This provision also requires FDA to post an annual summary report of the use of investigational drugs under the federal RTT pathway.

[52]Of the remaining 10 stakeholders we interviewed, officials from seven stakeholders told us they were not familiar with the federal RTT web page. We did not ask the other three stakeholders their views on the federal RTT web page because of the timing of those interviews relative to the timing of the launch of the new web page.

must provide access to their investigational drugs. Both added that FDA should more clearly communicate on the web page that there is no such requirement. In addition, officials from another stakeholder stated at the time of our review that FDA should explain on the web page the agency's role in implementing the federal RTT Act. In May 2019 FDA clarified on its web page that the federal RTT Act does not require manufacturers to provide patients access to their investigational drugs and that FDA's role includes posting a consolidated annual summary report on the use of investigational drugs through the federal RTT pathway.

Most Selected Manufacturers Communicated Whether They Consider Requests for Access to Investigational Drugs Outside of Clinical Trials and Conditions for Approval

Most of the 29 drug manufacturers in our review used their websites to communicate to patients and physicians whether they would consider individual requests for access to their investigational drugs outside of clinical trials. Among those that would consider requests, most also communicated the conditions under which they would review requests and grant access.

Manufacturers' consideration of requests for access. Our review of drug manufacturers' websites between January 31, 2019, and March 12, 2019, found that 23 of the 29 manufacturers in our review used their websites to communicate whether they considered individual requests for access to investigational drugs outside of clinical trials.[53] In communicating this information, 19 of the 23 manufacturers stated they were willing to consider requests, while the other four stated they were not considering requests.[54] The remaining six of the 29 manufacturers did not communicate information about whether they would consider requests for access to investigational drugs outside of clinical trials at the time of our review, but officials from all six told us they were in the process of developing content on this topic that they intended to post on their websites.

[53]Manufacturers used a variety of terms to characterize access to investigational drugs outside of clinical trials, such as "pre-approval access," "compassionate use access," and "early access."

[54]Eleven of the 19 manufacturers that stated on their websites that they did consider requests for access also made this information available to patients and physicians on the Reagan-Udall Expanded Access Navigator. See Reagan-Udall Foundation, *Expanded Access Navigator Company Directory*, accessed April 2, 2019, http://navigator.reaganudall.org/company-directory.

Information communicated by manufacturers that consider requests. Among the 19 manufacturers willing to consider requests for access to investigational drugs outside of clinical trials, all communicated on their websites that they required physicians to submit requests on behalf of their patients and provided information on how physicians should submit these requests. In addition, 18 manufacturers communicated an estimated time frame within which they would respond to requests.[55] The manufacturers provided additional information, including the following:

- Eighteen communicated information about the type of patient for whom they would consider granting access.
  - Eighteen stated that patients must have a serious or life-threatening disease or condition; have no comparable or satisfactory alternative therapies available; and be unable to participate in a clinical trial to be eligible to obtain access.
  - In addition, 17 stated that the treating physician must determine for the patient seeking access that the risk of taking the investigational drug is not greater than the anticipated benefit.
- Fifteen communicated other factors they would take into account during their review of requests. These factors included the following:
  - Ten stated that the supply of their investigational drugs was a consideration. That is, a manufacturer must have a sufficient supply of the investigational drug to support the drug's clinical development before granting access to patients outside of clinical trials.
  - Five referred to specific drugs to which they would consider granting access when describing the conditions under which they would consider reviewing requests. For example, one manufacturer stated that it would consider requests to access three of its investigational drugs (intended to treat bladder cancer, influenza, and HIV).
- One manufacturer communicated that after its initial review of individual requests, it uses an external advisory committee to further evaluate certain requests and ensure they are evaluated in an ethical and fair manner. The committee, which includes bioethical experts,

[55]The type of responses that drug manufacturers indicated they would give within these estimated time frames varied, including an acknowledgement of receipt and a decision about whether to provide access.

physicians and patient representatives, makes recommendations to the manufacturer about providing access to individual patients.[56]

- Many of the 19 manufacturers that communicated they were willing to consider individual requests for access stated that after they have approved a request they also required external entities to review the request. These included the following:
  - Thirteen stated they require the relevant regulatory authority to review requests. Of these, six specified that they require FDA to review requests for access in the United States. One of these six explained that it required a review by FDA to ensure all available safety data for the investigational drug were considered, and added that FDA is uniquely aware of such safety data.
  - Five stated they require the review of a research ethics committee or an IRB.[57]

Information communicated by manufacturers that do not consider requests. Among the four manufacturers that communicated on their websites they were not considering requests for access to investigational drugs outside of clinical trials at the time of our review, two provided reasons for their decision. Both cited safety concerns; for example, one explained that it wanted to ensure its investigational drugs were administered to patients only through clinical trials where safety could be closely monitored. One also cited limited resources, stating that it chose to focus its resources solely on conducting clinical trials. Both of the manufacturers that provided reasons for not considering requests for access communicated that they will periodically re-evaluate their policies.

Agency Comments

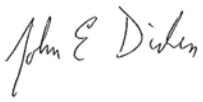
We provided a draft of this report to HHS for comment and HHS provided technical comments, which we incorporated as appropriate.

[56]In addition, this manufacturer communicated how many patients ultimately were granted access to an investigational drug outside of clinical trials. None of the other 18 manufacturers that communicated information about factors they take into account when reviewing requests also provided information on the number of patients for which they granted access to investigational drugs.

[57]A research ethics committee is a group of individuals who undertake ethical review of research involving humans, applying agreed on ethical principles.

We are sending copies of this report to the appropriate congressional committees, the Secretary of the Department of Health and Human Services, and other interested parties. In addition, the report is available at no charge on the GAO website at http://www.gao.gov.

If you or your staff have any questions about this report, please contact me at (202) 512-7114 or dickenj@gao.gov. Contact points for Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix I.



John E. Dicken
Director, Health Care

Appendix I: GAO Contact and Staff Acknowledgments

GAO Contact

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Staff Acknowledgments

In addition to the contact named above, Gerardine Brennan, Assistant Director; Pamela Dooley, Analyst-in-Charge; Craig Gertsch; Gay Hee Lee; and Moira Lenox made key contributions to this report. Also contributing were George Bogart, Laurie Pachter, and Ethiene Salgado-Rodriguez.

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For patients facing a serious or life-threatening condition who are unable to participate in a clinical trial and have exhausted all other options, FDA or the overseeing regulatory authority in your country may allow a licensed physician to provide their patient with an unapproved drug. In the U.S., this is called “Expanded Access” and elsewhere has been referred to as “Compassionate Use.” Additional information from the FDA is available here.

This policy applies to all personnel at Usona Institute who are involved with Expanded Access Use programs and activities. Request for unapproved use of any product which is already commercially available is outside the scope of this Policy.

Licensed physicians within the U.S. may submit expanded access requests to Usona. Requests for Expanded Access will be acknowledged within 5 business days of receipt. All Expanded Access use requests will be decided on a case-by-case basis at the sole discretion of Usona. All requests received will be reviewed anonymously by an internal Usona Committee

- The disease or condition for which use is requested is serious or life-threatening;
- The patient is ineligible or not able to participate in a clinical trial for the requested use and all approved treatment options have been exhausted without success and no satisfactory alternative treatment is available as determined by the requesting licensed physician;
- The requesting physician is a licensed physician and is authorized to deliver treatment as outlined in the request;
- There is sufficient clinical evidence to inform the safe use of the investigational drug under the requested use (at the requested dose and frequency of treatment);
- There is sufficient clinical evidence to suggest the requested use is expected to provide a potential clinical benefit to the patient (at the requested dose and frequency of treatment);
- The requested use would not negatively impact or interfere with active clinical trials or drug development programs of the applicable investigational drug;
- The treating physician has received approval by

Access Set and Setting Manual;

- There is an adequate supply of the requested investigational drug available for the requested use.

Please note that Usona is only able to respond to Expanded Access requests from licensed physicians.

The ClinicalTrials.gov listing for Usona's PSIL201 study is available here.

IMPORTANT: Do not include any Protected Health Information (PHI) identifiers in expanded access requests. Requests containing PHI will be immediately deleted.

Controlled Substances

Expanded Access requests of controlled substances are subject to additional restrictions. The licensed physician must actively maintain the required controlled substance license or must obtain such license (in applicable jurisdictions) prior to approval of the request and dispensation of investigational product. The physician must also agree to follow all applicable laws

safe use of these compounds. In order to be granted Expanded Access use of a psychedelic investigational drug by Usona, the treating physician must commit to following the conditions set forth in the *Usona Expanded Access Set and Setting Manual*. Physicians must have adequate resources, personnel and infrastructure to safely administer a psychedelic therapy and must have undergone specific training on the delivery of psychedelic therapies (for more information and requirements, see the *Usona Expanded Access Set and Setting Manual*).

Licensed physicians granted Expanded Access use of a Usona investigational drug are subject to additional terms, conditions and requirements, including a commitment to adequately monitor patient safety and to promptly report the results of expanded access use to Usona.

This policy is subject to revision at any time at the sole discretion of Usona. Usona is a not-for-profit organization and will not, under any circumstances, conduct a commercial outcome or a publicity outcome analysis for medication used under this program. Patient

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