Numinus

November 20, 2020

Patty Hajdu
Honourable Minister of Health
Health Canada
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Dear Minister Hajdu,

On behalf of the Numinus Wellness Clinical Advisory Board*, please find enclosed a briefing note and appendices making recommendations for the revision of Health Canada's Special Access Programme.

We would appreciate the opportunity to have a follow up call with relevant Health Canada staff to review these recommendations if this would be of assistance.

Sincerely,

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TITLE: Revising Health Canada's Special Access Program to Allow Pre-Approval Access to MDMA and Psilocybin

PREPARED FOR: Patty Hajdu, Honourable Minister of Health

DATE: November 20, 2020

ISSUE: There is a large and growing burden of mental illness affecting Canadians. In some cases, this is severe and can be life threatening for a range of reasons (e.g. opioid overdose, suicide). Existing treatments for severe mental illness are often ineffective and associated with unwanted side effects meaning new treatment modalities are urgently needed. A substantial body of research, including the completion of a growing number of randomized clinical trials, has demonstrated that psychedelic-assisted psychotherapy using psilocybin, MDMA and other substances is emerging as a novel approach for the treatment of a host of mental illnesses including treatment-resistant depression, post-traumatic stress disorder, substance-use disorder, and severe anxiety associated with a terminal diagnosis (see Appendix 2). These treatment modalities remain under investigation and are presently illegal in Canada, which presents a serious ethical concern, given that although phase III clinical trials are ongoing, including in Canada, patients who may benefit from pre-approval access through Health Canada's Special Access Programme are precluded from doing so as a result of current regulatory restrictions. This includes patients who have volunteered for, and graduated from, clinical trials in Canada and who may benefit from further treatment - and is not dissimilar to a volunteer to a cancer chemotherapy trial being unable to access ongoing investigational medication despite apparent clinical benefit once the trial is completed.

BACKGROUND: Historically, pre-approval access for medications in the drug development pipeline was possible through Canada's Special Access Programme. As summarized in a 2013 Canada Gazette (Vol. 147, No 22, October 2013), however, "The Government is concerned that the Special Access Programme (SAP) could be used to give individuals access to heroin, unauthorized products containing cocaine (benzoylmethylecgonine) and "restricted drugs" (defined in Part J of the FDR). Accordingly, amendments to the FDR and the *Narcotic Control Regulations* (NCR), with consequential amendments to the *New Classes of Practitioners Regulations* (NCPR), are needed to prevent access to these substances through the programme." While government regulations have been revised to enable legal access to heroin for medical purposes, access to psychedelic medications through the SAP remains not possible.

Importantly, the psychedelic substances being considered in research trials were unrelated to the focus on diacetylmorphine (heroin) which was the rationale for the change in 2013 whereas the removal of psychedelic medicines from the Special Access Programme could be viewed as totally unrelated (and inappropriate given existing research). Specifically, when the change to the Special Access Programme was made in 2013, decades of clinical research into psychedelic substances had been completed and there were already a large number of clinical trials demonstrating the safety and likely benefits of psychedelic-assisted psychotherapy (Appendix 2). Additionally, in certain Indigenous cultures (e.g. Mazatec people of Mexico), psychedelic

substances, such as psilocybin mushrooms, have been used in traditional medicine contexts for centuries and used recreationally without documented concerns (1). Lastly, there is growing recognition of stigma and racial discrimination as underpinning drug policies in North America (i.e. laws not based on clinical or public health evidence) and revisiting access to psychedelic assisted psychotherapy is therefore timely.

Since the above mental health conditions are often life threatening and existing treatments have major limitations in terms of success rates and side effects, Canadian citizens suffering with these conditions and who have exhausted conventional treatments would benefit from strategies that enable access to psychedelic-assisted psychotherapy prior to full approval by Health Canada while these drugs remain in clinical trials.

Recent approval of Section-56 exemptions for Canadians suffering with anxiety associated with terminal diagnoses to lawfully access psilocybin represents a positive step forward for Canadians who wish to access potentially life saving therapy; however, Section-56 exemptions do **not** account for two very important considerations regarding safety:

1. Access to a safe supply of psilocybin (including natural sources) that does not involve obtaining the drug from the unregulated illicit market
2. Parameters delineating the context in which the drug will be administered, which is critical for psychedelic substances due to drug interactions and other concerns (Appendix 1)

In the above context, clinical scientists have developed a knowledge base and best practices regarding methodologies for safe and effective delivery of psychedelic-assisted psychotherapy. Importantly, psychedelic-assisted psychotherapy is distinct in many ways and requires special attention to the context of delivery for safety and efficacy. Specifically, psychedelic medicines can not be considered in the same way as many pharmaceutical drugs, since effective treatment combines the psychedelic drug experience with a carefully established psychotherapeutic protocol involving:

1. Qualified mental health providers
2. Screening parameters for appropriate candidates for treatment including ensuring patients are not using other substances including medications that may lead to negative drug interactions
3. Psychological preparation sessions prior to psychedelic-assisted psychotherapy
4. Special considerations for the psychedelic-assisted session including the physical setting while under the influence of the medication
5. Psychological integration sessions and follow up in the weeks following the psychedelic-assisted psychotherapy session
6. Often, consideration for multiple psychedelic sessions (e.g. a month apart) as research (see appendix 3) has demonstrated that repeated sessions are often more effective than single sessions

Currently, the two drugs in development that show promise when combined with psychotherapy for the aforementioned mental health conditions are psilocybin and MDMA, both of which are restricted under the Food and Drug Act *Schedule J* and therefore may not be accessed through

the Special Access Programme. Given that both MDMA and psilocybin are already currently being developed for clinical trials, and are therefore accessible, and that there is a high burden of illness affecting Canadians for the aforementioned conditions, the Special Access Programme represents the most appropriate route for access that would ensure safe supply of the drug and, with additional parameters being set (Appendix 1), to appropriate clinical settings where the drug-assisted psychotherapy protocols could safely take place.

RECOMMENDATION: We recommend that the Health Canada Special Access Programme be revised so as to allow for consideration of applications for access to MDMA- and psilocybin-assisted psychotherapies via the Special Access Programme mechanism.

We also recommend that the Special Access Programme further develop a process for approving SAP requests that considers the following elements to ensure safety:

- Description of how the medication will be obtained (allowing for both synthetic and natural forms of psilocybin given Indigenous traditional practices) and safely stored prior to clinical use
- Description of the psychotherapy modality (e.g. motivational enhancement), including a brief description of the preparatory psychotherapy and post psychedelic psychotherapy integration, as well as the necessary training and credentials of who will be providing the psychotherapy
- Description of an appropriate location where the psychedelic-assisted psychotherapy will be safely provided with consideration given to ensuring patient safety while under the influence of the medication

A draft proposed Special Access Programme considerations template (Appendix 1), a summary of published literature (Appendix 2), and PDFs of relevant literature (Appendix 3) are attached for your interest. Given the known safety of MDMA and psilocybin that has been demonstrated in clinical trials (Appendix 2), returning MDMA and psilocybin into the purview of the Special Access Programme will reduce stigma towards this increasingly proven medical approach while also ensuring patient and public safety as these substances remain under consideration for therapeutic use using traditional sources (e.g. psilocybin mushrooms), or in the traditional drug development pipeline. This approach further enables increasing Canadian access to these potentially life-saving therapies in a context of growing morbidity and mortality from serious mental illness in Canada.

Appendix 1

Elements to be considered for Safe and Evidence-Based Delivery of MDMA- or Psilocybin-Assisted Psychotherapy:

Check	Safety Issue	Considerations
	Qualified care team	Prescribing primary care or specialist providers possess psychotherapy training and experience and/or collaborate with trained psychotherapist for treatment delivery
	Patient screening considerations	● Demonstrated need ● Failure of existing therapies ● No contraindications ● Consideration of personality characteristics likely to respond to therapy ● Risk of drug interactions with serotonergic drugs and/or natural health products addressed
	Psychotherapeutic protocol	Psychotherapy approach based on established protocol including preparatory and post-psychedelic integration
	Considerations to medication dosing and storage	Safe dosing and source of medicine including respecting Indigenous traditions and allowing for naturally sourced or synthetic psilocybin. Safe storage plan to avoid diversion.
	Considerations to safe psychotherapeutic setting	Safety considerations including: ● the utilization of a psychotherapy team for the psychedelic psychotherapy session ● adequate monitoring and recording of the session for accurate medical record keeping according to established protocols
	Course of treatment	Consideration given to the possible need for repeated medication and psychotherapy administration sessions

Appendix 2. Effectiveness and Safety Data for Psilocybin- and MDMA-Assisted Psychotherapy

A growing body of research and evidence from randomized clinical trials (RCTs) lend mounting support to the safety and efficacy of psychedelic-assisted psychotherapy. The most significant data exist for psilocybin- and MDMA-assisted psychotherapy for which the US Food and Drug Administration (FDA) has granted "Breakthrough Therapy" designation for treatment-resistant depression and posttraumatic stress disorder (PTSD), respectively (2,3).

Psilocybin Effectiveness:

Evidence indicates that psilocybin-assisted psychotherapy holds considerable promise for promoting long-term relief from depression and anxiety (4–6). Between 1960 and 2017, 11 clinical trials involving 445 participants with a life-threatening disease demonstrated significant reductions in symptoms of depression and anxiety, highlighting the overall safety and efficacy of classical psychedelics, such as psilocybin (7,8). The potential therapeutic benefits of psilocybin-assisted psychotherapy appear to be long-lasting. For instance, RCTs observed large effect sizes sustained 4.5 years after a single dose of psilocybin delivered in the context of psychotherapy, whereby 60-80% of participants with cancer-related existential distress had clinically significant reductions in depression and anxiety (9–11). Another double-blind controlled study of a single moderate dose of psilocybin in patients with advanced-stage cancer revealed lasting reductions in anxiety and a positive trend toward improved mood at 3- and 6-months follow-up (12). Similarly, a recent RCT found psilocybin-assisted psychotherapy was efficacious in producing large, rapid, and sustained antidepressant effects in patients with major depressive disorder (6), building upon open-label trials of psilocybin-assisted psychotherapy for treatment-resistant depression that observed rapid and sustained improvements in depressive symptoms 6 months following two psilocybin treatment sessions with psychological support (13,14).

In the context of tremendous and growing harms related to substance use in Canada, psilocybin-assisted psychotherapy has also demonstrated efficacy in recent clinical studies for the treatment of substance use disorders, such as nicotine and alcohol use disorders (15). An open-label pilot study at Johns Hopkins for tobacco smoking cessation demonstrated high success: 80% abstinence rates were observed at six months follow-up after two or three doses of psilocybin in combination with Cognitive Behavioural Therapy among individuals who smoked on average 19 cigarettes a day for an average of 31 years at baseline (16); at one year follow-up 67% remained abstinent (17). Promising preliminary results were observed in another pilot study of psilocybin-assisted psychotherapy for alcohol use disorder, with significant increases in abstinence rates and reduced craving following one or two psilocybin sessions in addition to weekly Motivational Enhancement Therapy over a nine-month follow-up period (18).

The consistency of clinical findings, alongside substantial evidence generated from large populational studies of citing related potential health benefits (e.g., associations with reduced opioid use disorder, suicidality/psychological distress, recidivism and intimate partner violence) (19–26), has encouraged the development of larger clinical trials to assess the therapeutic uses of psilocybin, including for other substance use issues such as stimulant use disorder (27).

Psilocybin and Psilocin Safety:

Over the course of its clinical development, thousands of participants have received psilocybin under controlled conditions in clinical settings for various indications, with subsequent results showing psilocybin to be well-tolerated, even at high doses (28–30). In recently published research studies that delivered psilocybin in specially constructed supportive settings that adhere to safety guidelines (31,32) - considering a range of factors such as careful screening, preparation, integration, dosing/drug interactions, qualified care team and supportive physical and interpersonal environment (see Appendix 1) – no serious adverse events have occurred (4,5,7,30,33–40). Possible adverse effects cited in the literature associated with classic psychedelics administered in clinical settings appear to be transient and non-serious including: anxiety, nausea/vomiting, mild increases in blood pressure and heart rate, and headache; no cases of psychosis or hallucinogen persisting perception disorder have been reported in modern trials using psilocybin (4,5,8,30,41–43). A meta-analysis of 8 double-blind placebo-controlled studies including 110 healthy subjects who received 1-4 oral doses of psilocybin found no cases of prolonged psychosis (35). Psilocybin is not associated with disease to any organ or system, has extremely low toxicity and dependence potential, and carries a very low risk for any long term physical, psychological or social harms (34,35,41,44–46). Additionally, as noted above, in certain Indigenous cultures (e.g. Mazatec people of Mexico), psychedelic substances, such as psilocybin mushrooms (containing both psilocybin and psilocin), have been used in traditional medicine contexts for centuries without reports concerning safety. Further, a peer-reviewed report commissioned by the Netherlands Minister of Health examining recreational use concluded “the use of magic mushrooms is relatively safe as only few and relatively mild adverse effects have been reported”(1).

MDMA Effectiveness:

Several decades of controlled clinical trials and a host of other human research have consistently shown benefit and demonstrated the safety and feasibility of MDMA-assisted psychotherapy. In the early era (1977-1985) of clinical study of MDMA (when it was still legal), approximately 4000 psychiatrists and psychologists administered MDMA to an estimated 500,000 patients in the context of psychotherapy without evidence of harm (47,48). In recent years, six phase 2 randomized clinical trials (RCTs) have been completed (49), signaling the exceptional promise of MDMA to enhance traditional psychotherapy. For instance, after undergoing MDMA-assisted psychotherapy, almost 70% of first responders and veterans initially suffering from treatment-resistant PTSD no longer met clinical criteria for the disorder at 12 months follow-up (50). MDMA research is now underway in over 16 international jurisdictions (51) with active phase 3 RCTs ongoing in Canada, the US and Israel (2). Of note, interim analysis of the first phase 3 RCT, requested by the FDA due to COVID-19, has demonstrated greater than 90% probability that the intervention effects will be statistically and clinically significant precluding the need for further enrollment (52). MDMA-assisted psychotherapy has shown consistent safety when used clinically (49,53). While two selective serotonin reuptake inhibitors (SSRIs) have been approved for PTSD (Sertraline and Paroxetine), analyses comparing data used for the approval of Sertraline and Paroxetine and pooled data from phase 2 studies indicated that MDMA-assisted psychotherapy may constitute “a substantial improvement over available pharmacotherapies in terms of safety

and efficacy" (2). As such, the intervention has proven consistently effective and safe, and represents a cost-effective (54) and highly promising opportunity to implement a novel enhancement to psychotherapy for PTSD (48).

MDMA Safety:

Safety data from studies in controlled research settings show that MDMA produces effects that are transient and well-tolerated by healthy individuals, including modest, self-limiting increases in body temperature, heart rate, and blood pressure. Common reactions were diminished as the drug is metabolized during treatment sessions over the next 24 hours, and in controlled clinical settings there have been no published or reported unexpected severe adverse reactions to date (expected adverse reactions have been rare and non-life threatening - and, as noted above, less severe than adverse reactions to Sertraline and Paroxetine) (55–62).

The efficacy and safety profile data (adverse event rates, physiological vital signs, and severity of suicidality) from six phase 2 studies conducted in the USA, Canada, Israel were submitted to the FDA and supported expansion of the drug development program into phase 3 trials (2,49,51). Further, MDMA in the context of psychotherapy was found to have a low potential for abuse (62). Overall, safety outcomes from clinical trials have been favorable and suggest that MDMA-assisted psychotherapy in controlled, supportive settings is a physiologically and psychologically safe, effective and durable treatment for participants with PTSD and who have been adequately screened for medical conditions (49,51,53,62).

Collectively, the above research clearly demonstrates both the consistently positive evidence of effectiveness of MDMA and Psilocybin Assisted Psychotherapy as well as their overall excellent safety profile when used in clinical settings.

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Appendix 3. Top published articles on MDMA- and Psilocybin-Assisted Psychotherapy

[Attached as a PDF]

Psychedelics and Psychedelic-Assisted Psychotherapy

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Objective: The authors provide an evidenced-based summary of the literature on the clinical application of psychedelic drugs in psychiatric disorders.

Methods: Searches of PubMed and PsycINFO via Ovid were conducted for articles in English, in peer-reviewed journals, reporting on "psilocybin," "lysergic acid diethylamide," "LSD," "ayahuasca," "*3,4*-methylenedioxymethamphetamine," and "MDMA," in human subjects, published between 2007 and July 1, 2019. A total of 1,603 articles were identified and screened. Articles that did not contain the terms "clinical trial," "therapy," or "imaging" in the title or abstract were filtered out. The 161 remaining articles were reviewed by two or more authors. The authors identified 14 articles reporting on well-designed clinical trials investigating the efficacy of lysergic acid diethylamide (LSD), *3,4*-methylenedioxymethamphetamine (MDMA), psilocybin, and ayahuasca for the treatment of mood and anxiety disorders, trauma and stress-related disorders, and substance-related and addictive disorders as well as in end-of-life care.

Results: The most significant database exists for MDMA and psilocybin, which have been designated by the U.S. Food and Drug Administration (FDA) as "breakthrough therapies" for posttraumatic stress disorder (PTSD) and treatment-resistant depression, respectively. The research on LSD and ayahuasca is observational, but available evidence suggests that these agents may have therapeutic effects in specific psychiatric disorders.

Conclusions: Randomized clinical trials support the efficacy of MDMA in the treatment of PTSD and psilocybin in the treatment of depression and cancer-related anxiety. The research to support the use of LSD and ayahuasca in the treatment of psychiatric disorders is preliminary, although promising. Overall, the database is insufficient for FDA approval of any psychedelic compound for routine clinical use in psychiatric disorders at this time, but continued research on the efficacy of psychedelics for the treatment of psychiatric disorders is warranted.

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"Timothy Leary's dead…"

—The Moody Blues, 1968

Although hallucinogens derived from plants have been used in religious practices for centuries, it was not until 1938 that the Swiss chemist Albert Hofmann synthesized the first synthetic hallucinogen, lysergic acid diethylamide (LSD), while working with the pharmaceutical company Sandoz (1, 2). On April 16, 1943, during a series of experiments, Hofmann serendipitously came into physical contact with LSD, which resulted in "an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colors" (1). In 1947, Sandoz began to market LSD under the trade name Delysid as an adjunctive psychotherapy medication and as an agent for experimental study on the nature of psychoses (1).

In 1960, Harvard psychologist Timothy Leary began experiments under the Harvard Psilocybin Project to determine whether psilocybin was an effective adjuvant agent in psychotherapy. Leary also experimented with LSD and eventually became a polarizing figure who was dismissed from Harvard, along with his colleague Richard Alpert, in 1963. The last of the Sandoz patents for the production of LSD expired in 1963, and illicit production of LSD increased as it was being used widely in medically unsupervised settings (1). In 1965, governments in Europe and the United States raised concerns about the general public's use of LSD and psilocybin. The U.S. Congress passed the Drug Abuse Control Amendments, which made the sale and manufacture of LSD without a license a misdemeanor and forced all researchers who had not been granted Investigational New Drug exemptions by

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the U.S. Food and Drug Administration (FDA) to relinquish their supplies of LSD (1). Clinical experimentation and research with psychedelics consequently decreased and were ultimately halted by the Controlled Substances Act of the Comprehensive Drug Abuse Prevention and Control Act of 1970.

Although Timothy Leary died in 1996, the lyrics by Ray Thomas of the Moody Blues almost three decades earlier were prescient: psychedelic research was indeed dead after the passage of the Controlled Substances Act. The following year, President Richard Nixon declared the "War on Drugs," and much of the experimentation in psychedelics moved underground in counterculture movements that spread across the United States and Europe.

Over the course of the past decade, there has been a resurgence of research on the potential therapeutic benefits of psychedelic compounds, with the number of published review articles and clinical trial reports steadily increasing. Research on these compounds has been supported by diverse organizations ranging from the United Kingdom Medical Research Council, a nationally funded health agency, to the Multidisciplinary Association for Psychedelic Studies (MAPS), a nonprofit organization that was founded in 1986 to increase the knowledge base of psychedelic substances. Additional support has come from the Heffter Research Institute, a nonprofit scientific organization founded in 1993 that promotes research with the classic hallucinogens and related compounds, and the Beckley Foundation, a U.K.-based research and nongovernmental organization focused on pioneering psychedelic research and evidence-based drug policy reform. These organizations have helped fund many pivotal trials and often work with regulatory agencies, including the FDA and the European Medicines Agency, to ensure that studies conform to the requisite regulatory guidelines for eventual approval of clinical use. Contemporary psychedelic drug research has been conducted at leading academic research universities around the world, including Johns Hopkins University, New York University, University of California, Los Angeles, Imperial College London, University of Zurich, and University of Basel. Recently, Johns Hopkins University and Imperial College London established centers for psychedelic research, which aim to investigate the effects of psychedelic drugs on the mind, the brain, and psychiatric disorders.

The U.S. Drug Enforcement Administration (DEA) currently classifies LSD, ayahuasca, psilocybin, and *3,4*-methylenedioxymethamphetamine (MDMA) as Schedule I substances, reflecting a lack of any accepted medical use or safety data and their potential for abuse. This review is intended to summarize the evidence base, including all of the available research in the scientific literature, for the safety and efficacy of psychedelic compounds in the treatment of psychiatric disorders.

METHODS

Searches were conducted of PubMed and PsycINFO via Ovid for English-language articles in peer-reviewed journals reporting on "psilocybin," "lysergic acid diethylamide," "LSD," "ayahuasca," "3,4-methylenedioxymethamphetamine," and "MDMA," in human subjects, for publication dates from January 1, 2007, through July 1, 2019. We chose to focus the review on these four compounds because they have recently received notable media coverage for their therapeutic potential (3–5). A total of 1,603 articles were identified and screened. Articles that did not contain the terms "clinical trial," "therapy," or "imaging" in the title or abstract were filtered out, resulting in a total of 161 articles for further review. To achieve a comprehensive summary of relevant clinical findings, our summary was not limited to these randomized clinical trials but also included open-label trials and investigations in healthy volunteers. We identified 14 articles reporting on well-designed clinical trials investigating the efficacy of LSD, MDMA, psilocybin, and ayahuasca for use in the treatment of mood and anxiety disorders, trauma- and stress-related disorders, and substance use disorders as well as for end-of-life care. Methodological strengths and limitations of studies evaluating the use of psychedelics in psychiatric disorders were identified and are summarized below for each drug. The review has been supplemented with information from texts on the history of the use of psychedelics in psychiatry and information on clinical techniques used in studies, such as psychedelic psychotherapy. Information about ongoing or planned clinical trials has been included with ClinicalTrials.gov registration information. The methodology flow chart is presented in the online supplement.

PSYCHEDELIC COMPOUNDS

The psychedelics can be divided into four classes based on their pharmacological profiles and chemical structures: classic psychedelics (serotonin 2A [5-HT_{2A}] receptor agonists), empathogens or entactogens (mixed serotonin and dopamine reuptake inhibitors and releasers), dissociative anesthetic agents (*N*-methyl-D-aspartate [NMDA] antagonists), and atypical hallucinogens, which affect multiple neurotransmitter systems (6). In this review we discuss three classic psychedelics (LSD, psilocybin, and ayahuasca) and one entactogen (MDMA) in detail. The dissociative anesthetic ketamine has been the subject of previous publications from the American Psychiatric Association Work Group on Biomarkers and Novel Treatments (7, 8) and will be compared and contrasted with these compounds in the section comparing the psychedelic compounds later in the review.

Psilocybin

Psilocybin is a plant alkaloid derived from tryptamine precursors and found in a variety of mushroom species (9). It has been used by native peoples of Central and South America within a sacramental context for centuries to facilitate spiritual experiences (10). In the 1950s, psychedelic mushrooms were introduced to Western culture when amateur mycologist R. Gordon Wasson and his wife, pediatrician Valentina Wasson, published a story in *Life* magazine describing their experience with psilocybin during participation in a Mazatecan ceremony in Mexico. The psychoactive compounds psilocybin and psilocin were first isolated from

the mushroom species *Psilocybe mexicana* through collaborative research by mycologist Roger Heim and Albert Hofmann and his colleagues at Sandoz Laboratories (1). After determining the molecular structures of these compounds, Sandoz began the synthetic chemical production of psilocybin, eliminating the previously required cultivation of mushrooms (1).

Psilocybin is actively metabolized to psilocin, a serotonin transporter inhibitor and 5-HT_{2A} receptor partial agonist with <40% activation efficacy; it also binds to the 5-HT_{2C}, 5-HT_{1A}, and 5-HT_{1B} receptors, with binding affinities in descending order (11, 12). When taken at high doses (0.3–0.6 mg/kg), it can cause mild to profound changes in sensory perception, including synesthesia, euphoria, sensory illusions, and auditory and visual hallucinations. These effects are dose dependent and last 3 to 6 hours (13–15). Unpleasant effects can include feelings of a seemingly "unending experience," as well as nausea, vomiting, and transient headaches (16–18).

Systematic investigation into psilocybin began in 1962, when Walter Pahnke and Timothy Leary conducted the "Marsh Chapel Experiment," also known as the "Good Friday Experiment" (19, 20). In this randomized controlled trial, Protestant divinity student volunteers (N=20; 10 per group) received psilocybin or a placebo (niacin) to evaluate the potential entheogenic properties of psilocybin. While the active and control drugs had differing physiological properties that likely challenged the blinding of the experiment, measurement of participants' responses with an eight-category scale for mystical experiences confirmed the hypothesized effect of psilocybin ($p<0.05$).

Leary and colleagues also conducted the "Concord Prison Experiment" to determine whether psilocybin-assisted group psychotherapy could reduce rates of recidivism after a period of incarceration (21). In this open-label study, prison inmates (N=32) participated in two psilocybin-assisted group psychotherapy sessions, each with a dose of 20–70 mg, followed by a series of psychotherapy sessions. Despite initial reports by Leary that psilocybin significantly reduced rates of recidivism, a later reanalysis by Doblin found that the recidivism rate of the experimental group was not significantly lower than that of the general prison population (20, 22).

Recently, there has been a resurgence in psilocybin research in the United States and Europe in the treatment of refractory mood disorders, refractory obsessive-compulsive disorder, end-of-life anxiety, and tobacco and alcohol use disorders. Carhart-Harris et al. (23) conducted an open-label pilot study evaluating the feasibility and efficacy of psilocybin-assisted psychotherapy for patients (N=12) with moderate to severe depression (defined as a score >17 on the Hamilton Depression Rating Scale [HAM-D]) and treatment-refractory depression (no improvement after trials of two different classes of antidepressant medication lasting at least 6 weeks within the current episode). Participants were given two oral doses of psilocybin in association with psychotherapy sessions, 7 days apart; they received a low dose (10 mg) of psilocybin at the first session and a higher dose (25 mg) at the second session. During the psilocybin sessions, therapists used a nondirective, supportive approach. All assessment measures were performed at baseline and at 1 week and 3 months after the second psilocybin-assisted psychotherapy session. The primary measure for efficacy was the Quick Inventory of Depressive Symptomatology (QIDS). QIDS depression scores were significantly decreased from baseline to 1 week and 3 months after treatment. The mean change in QIDS score was −11.8 (SD=4.9; p=0.002) at 1 week and −9.2 (SD=6.0; p=0.003) at 3 months. Secondary measures included the HAM-D and the Beck Depression Inventory (BDI). At the 1-week follow-up, categorical remission (defined as a score ≤9 on the BDI) was achieved by eight patients (67%). At the 3-month follow-up, categorical response (a 50% reduction in BDI score) was achieved by seven patients (58%), and five patients (42%) remained in complete remission.

In the same sample, functional MRI (fMRI) scans were performed at baseline and again the morning after the high-dose psilocybin-assisted psychotherapy session (24). One day before and 1 day after their psilocybin sessions, patients were shown images of faces with fearful, happy, or neutral expressions selected from the Karolinska Directed Emotional Faces set. Patients who received psilocybin showed increased amygdalar responses to fearful compared with neutral faces 1 day after treatment, and this response predicted positive clinical outcome 1 week later. Heightened amygdalar activity following psilocybin administration was interpreted as evidence of a different antidepressant mechanism of action than that of patients treated with selective serotonin reuptake inhibitors (SSRIs), who have shown diminished amygdalar response to emotional stimuli. Further fMRI research has demonstrated that psilocybin acutely disrupts default mode network connectivity, inducing temporary neuroplastic states that may make an individual more susceptible and receptive to cognitive functions and content accessed with coadministered nondirective supportive psychotherapy (25, 26).

Mood and adjustment disorders comorbid with cancer diagnoses are debilitating and are associated with poor clinical outcomes (27). Grob et al. (28) performed a randomized clinical trial (N=12, 11 of them women) investigating the safety and efficacy of psilocybin for the treatment of anxiety in patients with advanced-stage breast (N=4), colon (N=3), ovarian (N=2), peritoneal (N=1), or salivary gland (N=1) cancers or multiple myeloma (N=1). Each subject acted as his or her own control and had two treatment sessions in random order spaced several weeks apart: one session with a moderate dose of psilocybin (0.2 mg/kg) and the other with active placebo (niacin 250 mg). While there was no significant change in the self-reported State-Trait Anxiety Inventory (STAI) state score, STAI trait scores were significantly decreased at follow-up assessments 1 month (p=0.001) and 3 months (p=0.03) after the second treatment session. BDI

scores did not change from baseline (1 day before placebo administration) to the 2-week follow-up assessment, but they dropped significantly by 1 month (p=0.05) and remained significantly different at 6 months (p=0.03).

A similar but larger double-blind randomized crossover study by Griffiths et al. (18) (N=51) investigated the effects of psilocybin, administered in two sessions, on depression and anxiety syndromes in patients with terminal cancer who also had a DSM-IV diagnosis of an anxiety or mood disorder. The primary cancer types were breast (N=13), upper aerodigestive tract (N=7), gastrointestinal (N=4), genitourinary (N=18), hematologic malignancies (N=8), and other (N=1). Participants were excluded if they were taking psychoactive prescription medications (e.g., SSRIs, monoamine oxidase inhibitors, benzodiazepines). During the psilocybin sessions, participants received a high dose (22 mg/70 kg) or a low dose (1 mg or 3 mg/70 kg) of psilocybin, with the low dose serving as an active control. Participants were crossed over to receive the alternative dose in a second session 5 weeks later.

Before the first psilocybin session, participants met with study monitors to discuss "meaningful aspects" of their lives. During dosing sessions, therapists provided a supportive presence and encouraged participants to "trust, let go, and be open" to the experience, but otherwise were nondirective. The data showed that high-dose but not low-dose psilocybin produced large and significant decreases in depression and anxiety symptoms after 5 weeks, and this effect persisted through 6-month follow-up. A clinically significant response was defined as a decrease of ≥50% in score on the GRID-HAM-D-17 or the HAM-A relative to baseline, and scores below threshold level (≤7) defined symptom remission on each measure. The 6-month response rate was 78% for depressive syndromes using the GRID-HAM-D-17 and 83% for anxiety syndromes using the HAM-A; remission scores were achieved by 65% of participants on the GRID-HAM-D-17 and by 57% on the HAM-A.

A double-blind placebo-controlled (using niacin) randomized controlled crossover study by Ross et al. (29) (N=29) evaluated the efficacy of a single high dose of psilocybin (0.3 mg/kg) in conjunction with medication-assisted psychotherapy in patients with cancer-related anxiety and depressive symptoms as measured by the Hospital Anxiety and Depression Scale (HADS), with subscales for anxiety (HADS-A) and depression (HADS-D). Approximately two-thirds of the patients had advanced (stages II–IV) cancer, and the types of cancer included breast or reproductive (59%), gastrointestinal (17%), hematologic (14%), and other (10%). The BDI and the STAI state and trait scales were also administered at baseline and at regular intervals during the study. After 7 weeks, the placebo group was crossed over to psilocybin and the active psilocybin group to placebo. Medication-assisted psychotherapy included preparatory psychotherapy, medication dosing sessions, and postdosing integrative psychotherapy. During medication-assisted psychotherapy sessions, participants were encouraged to lie comfortably on a couch, to wear eye shades, to listen to preselected music, and to direct their thoughts toward their internal experience. Two study therapists, typically one male and one female, were present and available for psychological and medical support throughout the duration of the experimental sessions.

There were significant reductions in all of the primary measures (HADS total, HADS-A, HADS-D, BDI, STAI state, STAI trait) in the psilocybin group compared with the control group immediately after the experimental session, and these reductions were maintained until crossover of the control group at week 7. The psilocybin-first group had significant within-group reductions compared with baseline in anxiety and depression at all six time points, including the final time point at 26 weeks after dosing. Before being crossed over to psilocybin, the placebo-first group had no sustained significant reductions on any of the primary measures. Immediately after receiving psilocybin, the placebo-first group had significant within-group reductions in depression and anxiety symptoms on five of six primary measures. These reductions persisted and were present at all three time points, including the final time point at 26 weeks after dose 2 (approximately 6.5 months). At follow-up, 6.5 months after the active psilocybin intervention, 60%−80% of participants had sustained their responder status on depression and anxiety scales (defined as a reduction ≥50% in score on the measure compared with baseline).

There is preliminary evidence that psilocybin may be efficacious in the treatment of substance use disorders. An open-label study by Johnson et al. (30) enrolled participants who wanted to quit smoking (N=15) in a 15-week course of smoking cessation treatment coupled with psilocybin administration. The first 4 weeks of treatment consisted of cognitive-behavioral therapy, assigning a target quit date, and keeping a smoking diary. Psilocybin was administered at weeks 5 and 7, with an optional third psilocybin session at week 13. Participants were given a moderate dose of psilocybin (20 mg/70 kg) during the first experimental session and received a higher dose of psilocybin (30 mg/70 kg) at their second and third experimental sessions, unless they requested a moderate dose of psilocybin. The target quit date coincided with the first psilocybin session. During the sessions, research staff provided nondirective interpersonal support and did not deliver smoking cessation–specific content. Smoking abstinence was verified at all data collection points using exhaled carbon monoxide (CO level ≤6 ppm) and urinary cotinine measurements (level <200 ng/mL). At the 6-month follow-up, 12 of the 15 participants (80%) were laboratory-verified as abstinent; 10 participants (67%) remained abstinent at 12 months, and nine (75%) at 2.5 years. The pilot study has been extended to include 95 participants and should be completed by 2021 (ClinicalTrials.gov identifier 01943994).

Bogenschutz et al. (31) evaluated open-label psilocybin for the treatment of individuals who met DSM-IV criteria for alcohol dependence and had at least two heavy drinking days

in the previous 30 days (N=10). Participants also received psychotherapy, which included 14 sessions: seven sessions of motivational enhancement therapy, three preparation sessions, two psilocybin-assisted psychotherapy sessions, and two debriefing sessions. Participants received their first dose of psilocybin (0.3 mg/kg) after their first four psychotherapy sessions and their second dose (0.4 mg/kg) after their next four sessions, which was followed by four more psychotherapy sessions.

The primary outcome measures were the Stages of Change Readiness and Treatment Eagerness Scale, the Alcohol Abstinence Self-Efficacy Scale, the Penn Alcohol Craving Scale, and the Profile of Mood States. Two therapists were present throughout the psilocybin sessions, and their interactions with the participants were supportive and nondirective. Abstinence was not biologically verified and was based on self-report. The study found that abstinence significantly increased after the first psilocybin session at 4 weeks and was largely sustained through 36 weeks. Bogenschutz et al. are currently conducting a randomized clinical trial investigating the efficacy of psilocybin for treating alcohol dependence. The study is projected to enroll 180 participants and is expected to be completed in 2020 (ClinicalTrials.gov identifier 02061293).

Central to psilocybin-assisted therapy is the notion that participant response correlates with a psilocybin-induced "mystical" or "spiritual" experience. In the studies described above, the investigators noted correlations between symptom reduction and the participants' appraisals of their psilocybin experiences as personally meaningful, as reflected by their scores on the 30-item Mystical Experience Questionnaire (MEQ-30) (18, 30, 31). The MEQ-30 is a validated measure of mystical experience (32) that assesses seven domains of mystical experiences: internal unity, external unity, noetic quality (feeling of perception or revelation during the experience), sacredness, positive mood, transcendence of time/space, and ineffability (difficulty of communicating or describing the experience to others) (33). Confirmatory factor analyses have demonstrated the reliability and validity of the instrument, and external and convergent validity have been demonstrated by latent variable scores positively predicting psilocybin-related changes in attitudes, behavior, and well-being (32).

Mystical experiences have many names—religious experiences, transcendental experiences, transforming moments, epiphanies—but are all characterized by personal transformations that lead to dramatic or "quantum" changes in a person's sense of self and behavior (34). In a prospective study, Griffiths et al. (34) examined the long-term effects of a psilocybin-related mystical experience in individuals with no prior use of psilocybin when combined with meditation or spiritual practices. The total scores on the MEQ-30 and the Spiritual Experiences Scale both indicated healthy psychological functioning at 6-month follow-up, with the intensity of the psilocybin-induced mystical experience making the most significant contribution to the effect.

Although practitioners recognize that the acute presentation of a psilocybin-intoxicated individual closely resembles psychosis, hallucinogens such as psilocybin are not thought to precipitate a new psychotic illness but rather may unmask a psychotic disorder in those who are susceptible (35, 36). In an analysis of 110 healthy study volunteers from 227 psilocybin administrations, researchers found no evidence of hallucinogen persisting perception disorder, prolonged psychosis, or other long-term impairment of functioning in any subjects (37). Much of the research on the sequelae from psilocybin and other classic psychedelic use is from studies that screen participants for a history of psychiatric problems, regulate the dosage of the drug, and administer the drug in a controlled setting. These safeguards are intended to minimize the potential for adverse events.

Contrast this with the potential effects of psilocybin in an uncontrolled community setting. In an online survey (38) of almost 2,000 people who answered positively to the question of whether, after taking psilocybin mushrooms, they "ever had a psychologically difficult or challenging experience (i.e., a bad trip)—that is, have you experienced significant fear, anxiety, or distress or anything else that you found psychologically difficult," 39% of respondents reported that the experience was one of the most challenging experiences of their lifetime. Twenty-four percent of participants reported psychological symptoms lasting 1 week or longer (i.e., fear, anxiety, depression, or paranoia), 10% reported persistent symptoms for more than 1 year, and 7.6% sought professional help for psychological symptoms. Although this online survey is not rigorous enough to serve as a guide for clinical practice, it nevertheless points out potential concerns with the use of psychedelics in uncontrolled settings (6).

In 2018, the FDA designated psilocybin a "breakthrough therapy" for treatment-resistant depression, giving it priority consideration in the regulatory process (39). At this time, Compass Pathways, a London-based life sciences company, is starting phase 2B clinical trials in Europe and North America in 216 patients across 12–15 research sites for treatment-resistant depression, with additional phase 3 studies (40–42). The Usona Institute, a U.S. nonprofit medical research organization, is also planning phase 2 and 3 FDA-registration multisite trials to investigate psilocybin as a treatment for depression, anxiety, and mood disorders associated with end of life (43). Two ongoing phase 2 randomized clinical trials are investigating psilocybin's effects in patients with a diagnosis of obsessive-compulsive disorder to replicate and extend the initial findings of a study by Moreno et al. (44) (published in 2006, outside the search date criteria for this review) (ClinicalTrials.gov identifiers 03300947 and 03356483). Additional studies are investigating psilocybin for the treatment of cocaine use disorder (ClinicalTrials.gov identifier 04052568), opioid use disorder (ClinicalTrials.gov identifier 04161066), anorexia nervosa (ClinicalTrials.gov identifier 04052568), and depression in early Alzheimer's disease (ClinicalTrials.gov identifier 04123314).

Lysergic Acid Diethylamide (LSD)

LSD is an ergot derivative best known for its ability to induce powerful psychedelic, spiritual, and mystical experiences (1, 45, 46). LSD has been described as a *psychoadjuvant* or "nonspecific amplifier of the unconscious," with effects that include weakening ego identification, accelerating and broadening thought processes and content, promoting novel thought associations, and modifying one's interpretations and understanding of relationships and objects (47–49). It can induce feelings of closeness to others, enhance emotional empathy, enhance sociality, and acutely impair fear recognition (50). At moderate to high doses, LSD enhances sensory perception, which can lead to illusions, dreamlike waking imagery, synesthesia, alterations in sound perception, and mystical experience (48, 51–53).

The hallucinogenic effects of LSD are thought to be mediated by several mechanisms: partial agonism at the 5-HT_{2A} receptor, binding to the 5-HT_{1A}, 5-HT_{2C}, and 5-HT_{2B} receptors (with affinity in descending order), and binding at dopamine D_2 receptors. It also causes glutamate release in the frontal cortex and increased functional connectivity and excitability in thalamic and cortical structures (11, 54–58). LSD does not interact with monoamine transporters and is more potently bound than all other tryptamines to the 5-HT_{2A} and 5-HT_{1A} receptors (11). Other pharmacodynamic and pharmacokinetic mechanisms of LSD have been extensively explored (59) but are outside the scope of this review.

Starting in the 1940s and continuing through the 1960s, there was a rise in the number of studies on potential uses of LSD in healthy volunteers as well as in treating psychiatric disorders (16, 60). Observed psychological outcomes were initially thought to mimic schizophrenia, suggesting LSD as a potential model for psychosis (1, 47, 61). Recent studies have shown that psychotic symptoms associated with LSD ingestion are more likely in healthy volunteers with premorbid schizoid and paranoid traits and persons with a family history of schizophrenia (62). A large epidemiologic study of 130,000 adults in the United States did not find a link between psychedelic use (including LSD and psilocybin) and mental health problems or suicidal behavior (63).

Studies have noted the experiential effects of LSD-induced behavioral changes in individuals with substance use disorders, and LSD has been recognized as a potential treatment for alcohol use disorder (64). Several research groups have described LSD's potential for symptom alleviation in individuals with mood disorders and in pain syndromes associated with end-of-life care (16, 45, 65). Although preliminary LSD trials produced generally positive outcomes, clinical research on the therapeutic use of LSD was cut short in 1968, when the Drug Abuse Control Amendments were modified to make possession of LSD a misdemeanor and the sale of LSD a felony. LSD is currently classified as a Schedule I drug under the Controlled Substances Act (66, 67).

Recently there have been a few small open-label studies outside the United States investigating LSD for the treatment of mood disorders, anxiety in the terminally ill, and migraine headaches (16, 68). A group of Swiss and German researchers, Gasser et al. (48), conducted a randomized controlled trial to examine the safety and efficacy of LSD-assisted psychedelic psychotherapy in patients with anxiety associated with medical disease (N=12), including malignancy, Parkinson's disease, celiac disease, and ankylosing spondylitis. The primary outcome measure was the STAI trait and state forms completed at baseline, at 1 week, and at 2-month and 12-month follow-ups. At baseline, all participants scored >40 on the STAI state and trait, and half met DSM-IV criteria for generalized anxiety disorder. Participants were tapered off of antidepressant and antianxiety medications and received psychotherapy supplemented by two LSD-assisted psychedelic psychotherapy sessions spaced 2 to 3 weeks apart. Eight participants received a moderate dose of LSD (200 μg), and four participants received a low dose (20 μg), which was intended to act as an active placebo.

At the 2-month follow-up, mean trait anxiety did not significantly change in the high-dose LSD group compared with the placebo group, but mean state anxiety was significantly decreased in the high-dose LSD group compared with the low-dose (placebo) group. Comparing trait and state anxiety scores at baseline with those at the 2-month follow-up yielded effect sizes of 1.1 and 1.2, respectively. All four participants in the low-dose (placebo) group experienced increases in trait anxiety over time, and two of them also had increases in state anxiety (69).

Swiss researchers Schmid and Liechti et al. (69, 70) reported on short-term and long-term follow-ups after healthy volunteers (N=16) were given a single moderate dose of LSD (200 μg) as part of a randomized double-blind placebo-controlled crossover study with two experimental sessions. During the experimental sessions, participants rested in hospital beds and had the option of listening to music on headphones (no alternative entertainment was offered, and no specific guidance or therapy was provided). Participants were asked to complete the Persisting Effects Questionnaire (71), the Mysticism Scale, lifetime version, the Death Transcendence Scale, and the NEO Five-Factor Inventory at study screening and again 1 month and 12 months after their LSD session.

One and 12 months after LSD administration, the Persisting Effects Questionnaire showed significant increases in positive attitudes about life or self, positive mood changes, altruistic/positive social effects, positive behavioral changes, and well-being/life satisfaction that participants attributed to their LSD experience. The Mysticism Scale total score was increased, with significant increases in introvertive and extrovertive factor scores. The Death Transcendence Scale total score and mysticism subscale scores were also significantly increased at 1 and 12 months, and the NEO Five-Factor Inventory ratings of conscientiousness were significantly higher at 12 months. After 12 months, 10 of 14 participants (71%) rated their LSD experience "among the 10 most meaningful experiences" in their lives, and five participants rated it "among the five most spiritually meaningful

experiences" in their lives. This study suggested positive effects of LSD on attitudes, mood, and behavior, which may have implications for the treatment of psychiatric disorders (70).

Neuroimaging researchers Mueller et al. (72) conducted a double-blind placebo-controlled randomized crossover study investigating the effects of LSD (100 μg) on amygdalar activity during processing of fearful stimuli in healthy subjects (N=20). At the point of anticipated peak effect, 2.5 hours after LSD ingestion, participants underwent fMRI scans while viewing images of faces depicting various degrees of fear, anger, happiness, or neutral expressions taken from the Ekman and Friesen series of Pictures of Facial Affect. All participants were crossed over to the other condition and scanned with the same protocol. Compared with placebo, LSD produced a significant decrease in left amygdalar reactivity to fearful stimuli and impaired recognition of fearful faces, but it did not affect recognition of neutral, happy, or angry faces. It was also noted that LSD administration was associated with decreased activity in the right medial prefrontal cortex compared with placebo. The investigators interpreted the results as indicating that LSD may modify the processing of biases toward negative stimuli, which play a role in depression and anxiety disorders. They also suggested that LSD might be useful for reducing perceptions of negative emotions, ameliorating social cognitive deficits, and facilitating therapeutic alliance.

Recently, there has been emerging interest in microdosing LSD, the practice of taking doses below the perceptual threshold at 3- to 5-day intervals in an effort to trigger a cellular response. Mainstream media publications and subjective reports have suggested that microdosing LSD at 10–20 μg might induce positive effects, such as promoting creativity and enhancing mood, without the full experience of psychedelic effects (73, 74). Currently, there is no available scientific evidence to support the practice of microdosing. In fact, LSD doses of 13 and 26 μg (N=20) have been shown to produce measurable subjective and physiological effects with minimal effects on cognition and creativity (75). It is worth highlighting that low-dose LSD (20 μg) received by the active placebo group in the Gasser et al. study mentioned (48) above was associated with worsening anxiety in people with comorbid medical illness. While this finding may be attributable to resampling over time or placebo nonexpectancy, it may also be ascribed to microdosing. The Beckley Foundation intends to study the neurobiological and clinical effects of LSD microdosing as a strategy for cognitive enhancement in an upcoming investigation, but specific details were unavailable at the time of writing.

While the current LSD clinical research is limited, there are several new clinical investigations on the horizon in Switzerland. These studies will examine LSD as a treatment for patients suffering from anxiety with or without a life-threatening disease (ClinicalTrials.gov identifier 03153579), LSD-assisted psychotherapy for patients with illness-related anxiety (ClinicalTrials.gov identifier 00920387), and LSD-induced altered states of consciousness (ClinicalTrials.gov identifier 03321136).

Ayahuasca

Ayahuasca is a decoction prepared through the combination of *Banisteriopsis caapi* and *Psychotria viridis*, two plants native to the Amazon basin (76–79). Ingested orally, the mixture is known to induce effects by actions of β-carboline alkaloids (namely, harmine derivatives) found in *Banisteriopsis caapi* and *N,N*-dimethyltryptamine (DMT) in *Psychotria viridis* (76, 78). The preparation works synergistically, in that β-carboline alkaloids inhibit monoamine oxidase A (MAO-A) (80), preventing peripheral degradation of DMT, a serotonin transporter and norepinephrine transporter inhibitor as well as releaser of 5-HT and agonist at 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_{2B} receptors (with affinity in descending order) (11, 80, 81). The environment in which the substance is ingested, the user's expectations, and pharmacodynamic interactions of the decoction's components are all thought to influence outcomes associated with ayahuasca ingestion (77).

Ayahuasca is associated with a wide range of subjective effects, including auditory and visual hallucinations, altered sensorium, altered spatial perceptions, and euphoria (77, 82), as well as mystical and noetic experiences (77). Psychotic episodes have been documented in association with ayahuasca intoxication, usually in persons with a personal or family history of mood disorders, psychotic disorders, or substance use disorders (36, 60, 83). These ayahuasca-induced psychoses are not generally prolonged. It has been documented that psychoses can be mitigated by screening individuals for preexisting psychiatric disorders, but conclusions regarding the relationship between ayahuasca and prolonged psychotic episodes are drawn from small sample sizes, therefore limiting generalizability (60, 84).

Ayahuasca consumption has been associated with traditional practices among indigenous groups of the northwestern Amazon region, but the past several decades have seen a growing international interest in its possible therapeutic effects (77, 85). The U.S. Supreme Court has sanctioned the use of ayahuasca for religious and spiritual practices (86) by groups such as União do Vegetal and Santo Daime, but clinical trials in the United States remain nonexistent because DMT, a component of ayahuasca, is a Schedule I controlled substance.

Clinical investigations with ayahuasca outside the United States have begun in the past several years. Brazilian researchers Osório et al. (87) conducted a small (N=6) open-label clinical trial investigating the efficacy of ayahuasca in patients with depression who had not responded to at least one trial of an antidepressant medication. All patients met criteria for major depressive disorder based on the Structured Clinical Interview for DSM-IV and were admitted to a psychiatric unit for 2 weeks for drug washout prior to ayahuasca administration. The HAM-D and Montgomery-Åsberg Rating Scale (MADRS) were administered 10 minutes

before ayahuasca administration and again 40, 80, 140, and 180 minutes afterward, with follow-up assessments 1, 7, 14, and 21 days later. Participants drank a standard dose (2.2 mL/kg) of ayahuasca (containing 0.8 mg/mL DMT, 0.21 mg/mL harmine, and no harmaline as measured by gas chromatography/mass spectrometry) prepared by the Santo Daime community. All participants were discharged from the psychiatric unit 24 hours after ayahuasca administration. Mean HAM-D score was reduced by 62% 1 day after drug administration (p=0.01), with an even more pronounced reduction of 72% (p=0.01) 7 days after drug administration. The mean MADRS score was reduced by 82% at 7 days (p=0.009), with a sustained effect at 21 days. Investigators noted that the most significant antidepressant effects were observed for expressed sadness, pessimistic thinking, suicidal ideation, and difficulty concentrating.

Given the positive therapeutic signal of their pilot study, the same research team conducted a replication study with a larger sample (N=17) (88). The mean baseline HAM-D score for this group was 19.4, and the mean baseline MADRS score was 25.6. Symptoms, as measured by both scales, significantly decreased acutely, starting 80 minutes after drug administration. At 21-day follow-up, the mean HAM-D score was 7.56, representing a highly statistically significant mean change of −11.4 points ($p<0.0005$). Positive findings in the earlier study were replicated, but because neither study was randomized, double-blinded, or placebo-controlled, the results must be viewed as preliminary. Although vomiting occurred in about half the participants, participants generally described the ayahuasca session as a pleasant experience, and no serious adverse events were observed in either study.

Currently, the data are insufficient to support the use of ayahuasca in the clinical setting. The clinical research involving ayahuasca, which includes promising preliminary results for the treatment of depression, is limited by several factors, including lack of chemical analyses to confirm the exact ingredients in the ayahuasca drink used in the studies. A multitude of additional compounds have been described across indigenous preparations, including, among others, caffeine, nicotine, cocaine, and scopolamine (78). In assessing the aforementioned studies, one must be cognizant of the fact that ayahuasca was administered as a nonstandardized concoction. Randomized clinical trials using pharmacologically pure compounds are necessary to advance our knowledge about the therapeutic potential of ayahuasca.

3,4-Methylenedioxymethamphetamine (MDMA)

MDMA is a ring-substituted phenethylamine with structural similarities to amphetamine and mescaline. MDMA was synthesized by Merck & Co. in 1912 as a potential therapeutic agent to decrease clotting time and to prevent hemorrhaging (89). The compound did not prove efficacious for use as a hemostatic drug, but its psychotropic properties were recognized. Chemist Alexander Shulgin resynthesized MDMA in 1976, and the first published report characterizing the psychoactive effects of MDMA appeared in 1978 (90).

Despite the lack of systematic research into its efficacy and safety, some psychotherapists began using MDMA to improve the outcome of psychotherapy sessions with the goal of enhancing their patients' insights and understanding of their psychological problems. MDMA was associated with feelings of emotional well-being and was described as "penicillin for the soul" (90).

These psychoactive properties encouraged MDMA's use as a recreational drug. In the early to mid-1980s, MDMA was illicitly synthesized and distributed under the street name "Ecstasy" and became popular for facilitating an altered emotional state at dance parties called "raves." Because of concerns about abuse liability and neurotoxicity, the DEA emergently classified MDMA as a temporary Schedule I substance in 1985, and then permanently classified it as such in 1988.

MDMA and other *3,4*-methylenedioxy- substituted phenethylamines have been postulated to represent a new class of pharmacological agents, termed entactogens, with effects only partially overlapping those of psychostimulants and serotonergic hallucinogens (91–93). The effects of MDMA are believed to be mediated by a number of mechanisms, including monoamine release, serotonin and norepinephrine transporter reuptake inhibition, monoamine oxidase inhibition, partial agonism of serotonin receptors (5-HT_{2A}, 5-HT_{1A}, and 5-HT_{2C} receptors), and increase in blood concentrations of oxytocin (94–98). To date, studies with healthy volunteers have confirmed that MDMA produces an easily controlled and reversible state of altered consciousness characterized by euphoria, empathy, well-being, insightfulness, extraversion, positive mood, gregariousness, feelings of authenticity, increased access to emotionally intense material, increased interpersonal trust, and compassion for oneself and others (96, 99–103). In the clinical population, anxiety has been reported in a majority of study participants, and painful emotions such as grief, fear, and rage are not uncommon in participants with a diagnosis of PTSD (104–106).

The first double-blind placebo-controlled MDMA study in the United States was conducted in 1994 (107) and was followed up by two additional phase 1 trials (91, 108). A single dose of MDMA causes transient but tolerable increases in heart rate, blood pressure, and body temperature in healthy subjects (109). Subsequent placebo-controlled studies in Europe confirmed these general safety and tolerability findings and demonstrated that the processing of contextual information is left intact after MDMA ingestion (110, 111).

A double-blind fMRI randomized clinical trial in healthy volunteers (N=9) (112) showed that during peak drug effect, MDMA decreased amygdalar reactivity in response to angry faces but not fearful faces and enhanced ventral striatum activity in response to happy faces from the Ekman and Friesen series of Pictures of Facial Affect. Volunteers receiving MDMA were also better able to verify positive facial expressions and found it more difficult to identify negative ones, compared with volunteers who received placebo. These findings of reduced response to threat and enhanced

responses to reward provided important insights into MDMA's effects on emotional information processing (112, 113).

In 2010, Mithoefer et al. (106) completed the first phase 2 randomized controlled trial investigating the efficacy of MDMA in treating chronic PTSD (N=23). The study enrolled adults with a DSM-IV-TR diagnosis of chronic PTSD. Inclusion criteria also included treatment-resistant symptoms (defined as a score ≥50 on the Clinician-Administered PTSD Scale [CAPS]) and previous failure of at least 3 months of an SSRI or selective serotonin-norepinephrine reuptake inhibitor in addition to 6 months of psychotherapy (the specific type of psychotherapy was not specified). Study participants received two experimental sessions of either manualized MDMA-assisted psychotherapy with active drug (125 mg orally with an optional supplemental dose of 62.5 mg) (N=12) or placebo (N=8). The manualized therapy was developed for the study based on principles of Holotropic Breathwork (114) and LSD psychotherapy (115), and it emphasized a nondirective supportive approach (104, 105).

The primary outcome measure was mean change in CAPS total scores measured at baseline, 4 days after each experimental session, and 2 months after the second experimental session. Baseline mean CAPS scores were 79.6 (SD=8.1) for the placebo group and 79.2 (SD=6.6) for the MDMA group (p=0.966). Three to 5 days after the first experimental session, the participants' CAPS scores were 74.1 (SD=10.3) for the placebo group and 37.8 (SD=8.4) for the MDMA group (p=0.013). Three to 5 days after the second experimental session, CAPS scores were 66.8 (SD=8.0) for the placebo group and 29.3 (SD=6.5) for the MDMA group (p=0.002). Two months after the second experimental session, CAPS scores were 59.1 (SD=9.4) for the placebo group and 25.5 (SD=7.7) for the MDMA group (p=0.013). A significantly greater proportion of the MDMA group (10 of 12, 83.3%) than the placebo group (2 of 8, 25%) met criteria for categorical response (reduction ≥30% from baseline in CAPS score). All placebo-treated participants were offered the option of subsequent open-label crossover. Seven of eight chose to cross over, and all seven had a clinical response 4–6 weeks after two MDMA sessions. The mean change in CAPS score in this group (N=7) was −31.7 (SD=15) ($p<0.05$).

CAPS scores obtained 17–74 months after the two MDMA-assisted psychotherapy sessions were examined in a prospective long-term follow-up study (116). Sixteen participants completed all measures over 3.5 years (duration of follow-up: mean=45.4 months, SD=17.3). Among completers, no significant change was observed in mean CAPS scores from the point of exit from the trial (mean=24.6, SD=18.6) to the final follow-up assessment (mean=23.7, SD=22.8). On average, the group maintained statistically and clinically significant PTSD symptom relief, suggesting a potential for durable therapeutic effect from MDMA-assisted psychotherapy.

Most recently, Mithoefer et al. (105) completed a three-dose phase 2 double-blind randomized controlled trial investigating the efficacy and dose-response relationship of MDMA-assisted psychotherapy for the treatment of chronic PTSD in service personnel, firefighters, police officers, and veterans (N=26). All participants had a diagnosis of PTSD for at least 6 months, had a baseline CAPS total score ≥50, and had failed to respond to, or tolerate, previous pharmacotherapy or psychotherapy trials. Participants were required to taper and remain off of psychotropic medications during study participation. Participants were randomly assigned to receive MDMA at a low dose (30 mg; N=7), a moderate dose (75 mg; N=7), or a high dose (125 mg; N=12) in two blinded psychotherapy sessions spaced 1 month apart. In all of the MDMA sessions, participants had the option of receiving a supplemental dose of half of the initial dose 1.5–2 hours after the initial dose. During the MDMA sessions, two therapists, a male and female co-therapy team, performed manualized MDMA psychotherapy (the same nondirective supportive therapy approach used in the pilot study described above). The primary outcome measure was the mean change in CAPS score from baseline to 1 month after the second experimental MDMA session. The moderate- and high-dose groups had significantly greater reductions in PTSD symptom severity from baseline than the low-dose group (low-dose group: −11.4, SD=12.7; moderate-dose group: −58.3, SD=9.8; p=0.0005; high-dose group: −44.3, SD=28.7; p=0.004). No significant differences were found between the moderate- and high-dose groups (p=0.185). Remission was achieved in six of the seven participants (86%) in the moderate-dose group and seven of the 12 participants (58%) in the high-dose group, compared with two of the seven participants (29%) in the low-dose group. Additionally, compared with the low-dose group, more participants in the moderate- and high-dose groups met criteria for clinical response (defined as a reduction >30% from baseline in CAPS score): 29% in the low-dose group, 100% in the moderate-dose group, and 67% in the high-dose group.

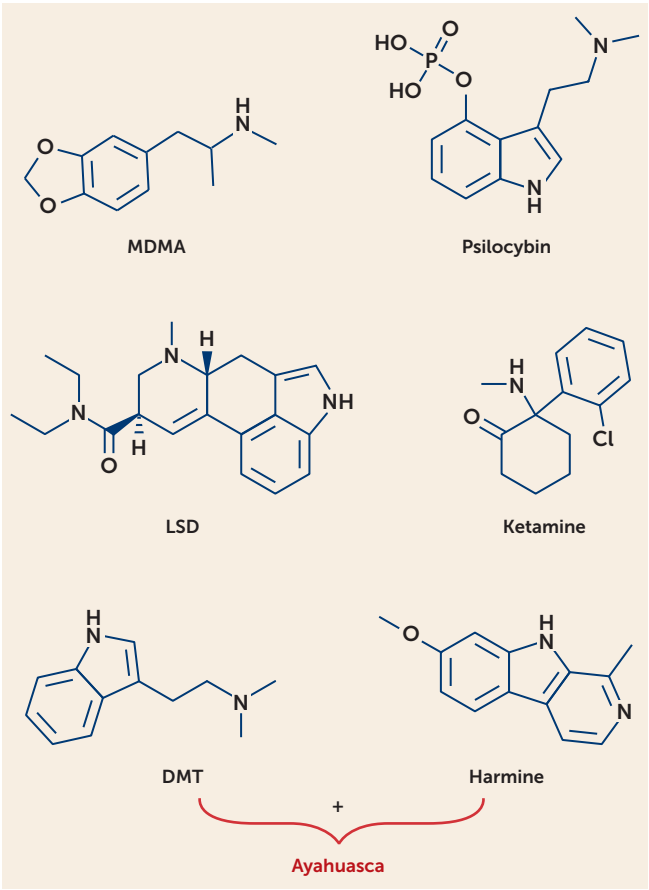
In 2016, the FDA approved the MAPS investigators' design for two phase 3 clinical trials investigating MDMA for the treatment of PTSD (117). In 2017, the FDA designated MDMA as a "breakthrough therapy" based on its use in assisting psychotherapy for the treatment of PTSD, giving it priority consideration in the regulatory process (118).

Additional trials investigating the efficacy of MDMA for social anxiety disorder in adults with autism spectrum disorder (ClinicalTrials.gov identifier 02008396) and for anxiety associated with a life-threatening illness (ClinicalTrials.gov identifier 02427568) have been completed but are outside the scope of this review.

COMPARISON OF THE PSYCHOLOGICAL EFFECTS AND NEUROBIOLOGY OF THE PSYCHEDELIC COMPOUNDS

The classic psychedelics are subdivided into phenethylamines and tryptamines. The tryptamines include the synthetic ergoline LSD as well as the plant-derived indoleamines psilocybin and DMT. The phenethylamines include MDMA

FIGURE 1. Molecular structure of psychedelic compounds[a]



[a] MDMA is a phenethylamine, psilocybin and DMT are indoleamines, LSD is an ergoline, and ketamine is a cyclohexanone. Molecular structures are from PubChem (National Center for Biotechnology Information, U.S. National Library of Medicine) and rendered in the ChemDoodle software program.

and mescaline. The tryptamines share their core structure with the neurotransmitter serotonin (5-HT) and modulate multiple targets, including 5-HT receptors, monoamine transporters, and trace-amine-associated receptors (11). The entactogen MDMA (a phenethylamine) is pharmacologically related to mescaline, amphetamine, and methamphetamine and acts as a serotonin agonist and releases both dopamine and norepinephrine (119). The dissociative anesthetic ketamine, which has psychedelic properties, is an NMDA receptor antagonist that has shown antidepressant efficacy across multiple clinical trials and efficacy in decreasing suicidal ideation (7, 8, 120). While not a classic psychedelic, ketamine can cause dose-dependent dissociation, alterations in the perception of sight and sound, derealization, "mystical-type" effects, paranoia, and transient confusion (121–124).

The molecular structures of MDMA, psilocybin, LSD, ayahuasca, and ketamine are depicted in Figure 1.

While the structures and pharmacological profiles of these compounds are distinct, the psychological effects overlap. Examples of the cognitive, perceptual, emotional, and social relatedness effects of the psychedelics, as well as their primary pharmacological mechanisms of action, are provided in Table 1, organized by compound as classified by Garcia-Romeu et al (6).

As shown in the table, some of the psychological effects of the classic psychedelic compounds, MDMA, and ketamine are similar, whereas the primary underlying neurobiological processes are distinct. These divergent pharmacological profiles provide an opportunity to understand the neurobiology of the different psychological effects and the potential to use these different psychological effects in the treatment of psychiatric disorders.

Among the classic psychedelics, LSD has the greatest affinity for the 5-HT_{2A} receptor (which is associated with psychoactive effects of the classic psychedelics), and only LSD binds with submicromolar affinity to the α_1 adrenergic and has affinity for the D_{1-3} dopaminergic receptors (11). Visual perceptual changes in study subjects who have ingested LSD are associated with increased functional connectivity in the visual cortex, and the effects on consciousness (i.e., sense of self) are correlated with decreased connectivity between the parahippocampus and retrosplenial cortex within the default mode network (125). Comparing this profile to the simple tryptamine psilocybin, LSD is 10 to 100 times more potent than psilocybin at the 5-HT_{1A} and 5-HT_2 receptors and is more potent at α adrenergic and dopaminergic receptors, whereas psilocybin is a more potent inhibitor of the serotonin transporter (11).

The entactogen MDMA overlaps in chemical structure with methamphetamine and mescaline and has the biological effects of epinephrine, dopamine, and serotonin (126). Derealization may occur in individuals using MDMA, but unlike the classic psychedelic compounds, hallucinations are rare (119). This pharmacological profile leads to psychological effects that overlap with those that occur with the serotonergic hallucinogens, including positive emotions and euphoria. MDMA shares the autonomic and cardiovascular effects of a methamphetamine, such as increased energy, tachycardia, increased systolic and diastolic blood pressure, and tachypnea. While MDMA has been singled out as an entactogen for its ability to create a feeling of closeness or connection with others and increasing emotional empathy (127), classic psychedelics also have the ability to increase feelings of openness and trust (128).

The dissociative anesthetics (ketamine, phencyclidine, and nitrous oxide) also have psychological properties in common with the classic psychedelics (see Table 1). In the majority of recent depression studies, ketamine has been administered by intravenous infusion at a rate of 0.5 mg/kg over 40 minutes without adjunctive psychotherapy (7). Recently, a subgroup of clinicians have been administering ketamine via sublingual or intramuscular routes, at relatively higher doses than previously reported in the literature, to treat a wide array of psychiatric illnesses, including depression, anxiety, PTSD, and existential issues. This technique has been termed ketamine-assisted psychotherapy. Ketamine-assisted psychotherapy is not currently well

TABLE 1. Primary pharmacological mechanisms of action of the psychedelic compounds and their cognitive, perceptual, emotional, and social relatedness effects[a]

Class and Compound	Primary Mechanism of Action	Effects					Other Compounds
		Cognition	Perception	Negative Emotions	Positive Emotions	Social Relatedness	
Classic psychedelics							
LSD, psilocybin, and ayahuasca (DMT)	Serotonin 5-HT_{2A} and 5-HT_{2C} receptor agonist	Increased cognitive flexibility (53), creative thinking (51), and insightfulness (52); distractibility and disorganized behavior (49, 51, 53, 62)	Changes in visual perception (51, 53); mystical experiences (6, 12, 34, 52); paranoia (53); hallucinations, depersonalization, derealization (51, 62, 69)	Anxiety (29, 51, 69); labile mood with anxiety (34)	Increase in well-being and life satisfaction (70); positive mood (60, 71) or blissful state (52, 53, 69)	Enhanced empathy (50); prosocial attitudes and behaviors (34); openness and trust (69)	Mescaline
Entactogens							
MDMA	Serotonin 5-HT_{2A} agonist; mixed serotonin, norepinephrine, and dopamine reuptake inhibition and release	Deficits in spatial memory (111); mild impairment on psychomotor tasks (92)	Changes in body perception, slight visual and auditory alterations, no hallucinations (92)	Distrust and hostility (103); anxiety (93, 101, 103, 105)	Increased trust and sense of a greater meaning in life (100); euphoria (92, 103) and well-being (92)	Increased connectedness toward others (91, 99, 102); increased empathy (96, 100, 103)	MDA, MDEA
Dissociative anesthetics							
Ketamine	NMDA antagonist	Deficits in vigilance, verbal fluency, delayed recall, and tests of frontal lobe function (121)	Derealization, depersonalization (8, 120, 121, 124); illusions in all sensory domains and perceptual alterations (121)	Amotivation, emotional dulling, hostility (121); anxiety (121, 123)	Improved mood (7, 8, 120, 123)	Emotional withdrawal (121)	Dextromethorphan, phencyclidine (PCP), and nitrous oxide

[a] The table lists the compounds covered in the review, organized by class. See Jungaberle et al. (100) for an excellent review comparing psychedelics and entactogens. The atypical psychedelics ibogaine, *Salvia divinorum*, atropine, and *Datura* are not included in the table and are not discussed in this review. LSD=lysergic acid diethylamide; DMT=*N,N*-dimethyltryptamine; MDA=*3,4*-methylenedioxy-amphetamine; MDEA=*3,4*-methylenedioxy-*N*-ethyl-amphetamine; MDMA=*3,4*-methylenedioxymethamphetamine; NMDA=*N*-methyl-D-aspartate.

defined, and there is limited objective evidence to support its use at this time (129).

Ketamine is an NMDA antagonist that causes an increased activation of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors and indirectly enhances dopaminergic (D_2) and serotonergic (5-HT_2) activity (130). Ketamine reduces the contribution of NMDA receptors to afferent information from internal and external sensory inputs and causes glutamatergic overactivity, and limbic cortical disinhibition indirectly enhances dopaminergic and serotonergic activity (130). While there has been debate on whether ketamine's acute antidepressant effect requires normal function of the endogenous opioid system (131) or opioid system activation, through direct and/or indirect action at the mu-opioid receptors (132), ketamine's dissociative effects are primarily attributed to its NMDA receptor antagonism (132).

Like ketamine, the classic psychedelics are also potent modulators of glutaminergic activity in prefrontal circuits (133). Vollenweider and Kometer (133) compared the classic psychedelic psilocybin with ketamine and showed that the drugs produced an overlapping set of psychological effects on the five-dimension Altered States of Consciousness Scale. Psilocybin showed dose-dependent (0.15–0.27 mg/kg by mouth) increases in the dimensions of visionary restructuralization (i.e., visual illusions and hallucinations) and oceanic boundlessness (described as a blissful state and experience of unity), whereas ketamine, in a dose-dependent manner (6–12 μg/kg per minute intravenously) influenced dimensions of anxious ego-disintegration (described as a sense of disembodiment and impaired self-control) as well as vivid imagery and changing meaning of percepts (i.e., visual restructuralization) and experience of unity (e.g., "oceanic boundlessness"). These researchers assert that there is a common mechanism of action that modulates glutaminergic transmission in the prefrontal-limbic circuit that leads to neuroplastic adaptations via the AMPA receptor, which are the basis for the antidepressant efficacy of both psilocybin and ketamine (133).

Despite knowledge about pharmacodynamic profiles of the psychedelics, there remains debate about how they alter consciousness and mood (11). Vollenweider suggests that psilocybin induces metabolic changes, including hyperfrontality (i.e., increased cerebral blood flow to the prefrontal cortex), and alters thalamocortical synaptic transmission through activation of 5-HT_{2A} receptors in the cortico-striato-thalamo-cortical loop (133–135). Vollenweider and his colleagues propose that the disruption of thalamic gating disables the filtering of sensory and cognitive information, which leads to perceptual alterations during the psychedelic

experience (35, 49, 134). Carhart-Harris and his colleagues suggest that psilocybin and other classic psychedelics are associated with hypofrontality (decreased blood flow to the prefrontal cortex) and decreased connectivity and neural activity in key regions of the default mode network immediately after drug administration (26). He proposes that these physiological alterations drive the mind toward a more primitive state of entropy or disorder that is suppressed during normal waking consciousness and allows for the disruption of stereotyped patterns of thought and behavior. As the mind becomes more flexible, the individual may challenge automatic thoughts and develop new perspectives (26).

The research-informed theories of Vollenweider and Carhart-Harris are not exclusive and raise new questions about the role of cerebral perfusion, thalamic gating, connectivity, and serotonin in psychiatric disorders. Furthermore, they demonstrate how the psychedelics' unique and diverse pharmacological profiles, which only partially overlap, may be utilized to better inform our understanding of neuroscience.

PSYCHEDELIC-ASSISTED PSYCHOTHERAPY

The number of studies using psychedelic-assisted psychotherapy has increased, leading to variable methodologies across studies. The two most widely utilized psychotherapy paradigms are psycholytic therapy and psychedelic therapy (16, 115). Psycholytic therapy, which evolved in Europe from the 1950s to the 1970s, took the form of psychoanalytically informed talk therapy with low to moderate doses of LSD (30–200 μg), which were administered over several sessions. The sessions were believed to offer greater access to the unconscious with the goal of facilitating a discharge of emotionally charged psychic tension (136). Psychedelic therapy, which developed simultaneously in the United States with the existential and humanistic schools of psychology, used preparatory therapy followed by one or several high doses of a psychedelic (>250 μg LSD) to create an "overwhelming and transcendent experience," which was then processed in integrative therapy after the drug-facilitated session (136). The goal was to gain novel insights into the patient's condition (136). The recent MDMA studies have used a hybrid of psycholytic therapy and psychedelic therapy, and the majority of recent psilocybin studies have implemented versions of psychedelic therapy, which has recently been closely aligned with transpersonal psychology (18, 23, 29, 104).

Psychedelic-assisted psychotherapy, which includes the spectrum of psycholytic and psychedelic therapy, typically employs three types of sessions: preparatory, medication (one to three sessions with moderate to high doses of a psychedelic), and integration sessions (137). During the preparatory sessions, the therapist or co-therapist team engages the patient to explore his or her life history and to help the patient understand his or her symptoms and intentions, with an emphasis on the potential for emotional and psychological growth. They also educate the patient about what to expect during the psychedelic session, and they work to develop a sufficient therapeutic alliance (3, 115). During the medication session, the patient is ideally accompanied by a male-female co-therapy team, which has been widely adopted in MDMA studies (104). The male-female co-therapist dyad maintains integrity and safety for the therapeutic relationship, which should not be underappreciated given the history of sexual abuse that occurred during psychotherapy with MDMA in the 1980s (138).

The psychedelic drug is administered in a comfortable room with a reclining chair or bed in an environment that is decorated and appointed so that it will feel familiar and not intimidating in the way a medical office or institutional laboratory might. After drug ingestion, the patient is encouraged to focus his or her attention inward and is offered the option of listening to music and wearing eye shades (3, 29, 104, 115). For the next 6–8 hours, the therapists listen empathically to the patient and maintain a nonthreatening, neutral therapeutic stance. The drug effects and the patient's thought content drive the experience. The therapists' goal is to facilitate a sense of safety, trust, and openness (3, 104). After the medication session, during the integration sessions, the therapists work with the patient to interpret the content of the psychedelic experience into meaningful long-term change through identifying insights or interpreting thoughts or ideas that arose during the psychedelic session (3, 115, 137).

Little is known about the intrapsychic processes and mechanisms by which psychedelic drugs are presumed to work in facilitating psychotherapy or general mental health. It is believed that the therapeutic effect is a result of the interaction between the drug and the mindset of the patient (together often referred to as "set"), the external conditions (often referred to as "setting"), and the therapist(s) (1, 104, 136). It is believed that a therapeutic set and setting make adverse outcomes less likely even when challenging and painful experiences arise. Furthermore, working through a painful experience is an important part of the therapeutic process, just as "peak mystical experience" can be, and should not be considered an adverse event.

Currently, it is unclear whether one psychotherapy approach is better than another. Psychedelics might be used to catalyze or augment widely accepted structured therapies, such as prolonged exposure therapy, cognitive processing therapy, and acceptance and commitment therapy, or less structured treatments, such as dynamic therapy and psychoanalysis. Furthermore, it is unclear whether it is the psychedelic drug itself, the psychedelic-assisted psychotherapy experience, or drug-facilitated enhancements in the therapeutic alliance that promote change (136). While a statistical association between mystical experiences and resolution of symptoms has been reported, the lack of qualitative analysis of various elements of individual psychotherapy sessions used in combination with psychedelic

drug sessions limits external validity and, in turn, our understanding of the cognitive or emotional processes that lead to favorable outcomes.

THE POTENTIAL FOR ABUSE

All the drugs reviewed here, except ketamine, are currently classified by the DEA as Schedule I controlled substances under the Controlled Substances Act. As noted earlier, this classification was created by the U.S. Congress in 1970 to diminish the availability of drugs of abuse: "Substances in this schedule have no currently accepted medical use in the United States, a lack of accepted safety for use under medical supervision, and a high potential for abuse" (139). Other drugs under this classification include heroin, marijuana, methaqualone, and mescaline. Psychedelic drugs have remained Schedule I drugs for almost 50 years. Ketamine is classified as a Schedule III substance, which is for drugs with an accepted medical use (e.g., anesthesia) and a potential for abuse.

In 2010, the United Kingdom's Independent Scientific Committee on Drugs published a study that directly addressed the prevalence and severity of adverse effects of potential drugs of abuse on a nine-category matrix of harm (140). They derived scores estimating the magnitude of overall harm to users (and to others) for each drug and substance of abuse. At the top of the list was alcohol, with a harm score of 72, followed by heroin, with a score of 55, then crack cocaine, with a score of 54. Benzodiazepines and ketamine both had a harm score of 15, and methadone's score was 13. Ecstasy, LSD, and psilocybin were at the bottom of the list with harm scores of 9, 7, and 5, respectively. This publication was extremely controversial, although not without support, and eventually led to the dismissal of the lead author, David Nutt, from Britain's Advisory Council on the Misuse of Drugs. In response to this criticism, Nutt and his colleagues refined their methodology and used a multicriteria decision analysis to again evaluate the harmfulness of drugs, both to the individual and to society (140). The results were similar, with alcohol, heroin, and crack cocaine having the highest overall harm scores and Ecstasy, LSD, and psilocybin ranking at the bottom of the list. Given that the societal harm scores were influenced by data from economic costs, health records, police records, and an expert group approach, their generalizability is limited by availability of the analyzed substances in specific countries.

A National Institute on Drug Abuse (NIDA) "DrugFacts" brochure states that certain hallucinogens (e.g., PCP) are potentially addictive and can produce drug cravings and tolerance over time (141). However, hallucinogens are not associated with uncontrollable drug-seeking behavior (141) and animals cannot be trained to self-administer hallucinogens (142). Other hallucinogens (e.g., DMT in the form of ayahuasca tea) do not lead to addiction or tolerance (141). Medical administration of hallucinogens should include careful consideration of the appropriate dosage, patient screening, and appropriate preparation of the patient, including preparation and follow-up of psychedelic-assisted psychotherapy sessions in accordance with an approved procedure based on research evidence (143).

Another NIDA DrugFacts brochure acknowledges research evidence of the abuse potential of MDMA in animals, albeit to a lesser degree than cocaine (144). While MDMA self-administration models in animals suggest patterns of episodic use at irregular intervals, the observed potential for abuse seems to be less than that for amphetamine and methamphetamine (145). The prospective long-term follow-up study of individuals with PTSD who received MDMA (N=19; described above [116]) reported that no study participants developed a substance abuse problem (with any illicit drug) during the follow-up period of 7–17 months, suggesting that, at least in research settings, MDMA can be administered with minimal risk that patients will subsequently seek out and self-administer "street Ecstasy." However, further evaluation of MDMA's long-term risks is needed (116).

Researchers at Johns Hopkins University recently evaluated the abuse potential of medically administered psilocybin (143) and determined that, if approved as a medication, psilocybin would be appropriate for Schedule IV classification. Other substances currently classified as Schedule IV include benzodiazepines and hypnotics with a relatively low potential for abuse and dependence.

The available evidence supports a plan for further research into the abuse potential of psychedelic compounds, with consideration of both their therapeutic potential and their risk of abuse or misuse. Future research on psychedelic compounds should include measures of drug-seeking behavior over time, urine drug screens to monitor illicit drug use, and efforts to determine which patient populations may be vulnerable to developing new (or to experiencing relapse of preexisting) substance use disorders.

RECOMMENDATIONS FOR FUTURE RESEARCH

With the increased interest in psychedelic research and the FDA's fast-tracking of psychedelic compounds, this would be an appropriate time for the National Institutes of Health, in conjunction with the FDA and other funding agencies, such as MAPS, the Usona Institute, and the Heffter Research Institute, to conduct a series of international symposia on clinical trial methodology in psychedelic drug research. Sellers et al. (119) reviewed the challenges inherent in conducting psychedelic research, and their analysis could serve as a road map for these meetings. They describe multiple confounders and biases in psychedelic trials. They highlight the difficulty in blinding; the lack of data on the acute and chronic dose response (as the drugs can have very different psychological effects at different doses); patient biases and expectancy (including in studies that include patients with prior hallucinogenic use and do not account for that in the analyses); highly selected patient populations, which limits generalizability; and the exclusion of patients with known

risk factors (e.g., personal or family history of psychosis), which limits the understanding of the true risks of the drugs in the routine clinical care of a psychiatric patient population.

Sellers et al. also express their concern that many of the studies' dependent variables, such as the Hallucinogen Rating Scale and Altered States of Consciousness Scale, are incompletely characterized and do not have established predictive validity or utility. They assert that many of the commonly used scales in these studies are not validated patient report outcome measures and have not been shown to be surrogate markers of any therapeutic outcome measure. This is a fair criticism of many of the scales. Some scales, however, such as the MEQ-30, have been validated in experimental studies with controlled doses of psilocybin (32), although even the MEQ-30 was validated using a narrow range of drug doses and was restricted to one hallucinogenic compound. More rigorous analysis of the treatment assessment scales is needed in order to qualify them as patient report outcome measures in clinical trials.

Research will also be limited by the fact that there is not currently a rigorous definition of some of the clinical techniques used in these trials (e.g., psychedelic-assisted psychotherapy) and that expectations and the participants' prior drug experiences are important variables in the response to psychedelic-assisted therapy (6). Future research should also focus on the pharmacodynamic and pharmacokinetic profiles of these agents, with close attention paid to the dose-response relationship and side effects.

Finally, more studies focusing on abuse potential are needed, particularly as the potential for abuse relates to more vulnerable populations. Such studies will be important in assessing the risk these drugs may pose in routine clinical use and could be instrumental in meeting FDA requirements for changing the classification of psychedelics (119).

CONCLUSIONS

The published scientific evidence, although somewhat limited (Table 2), supports continued investigation of psychedelic compounds for treating psychiatric disorders, but it does not yet support the use of any of these drugs for patient care by clinical practitioners outside the research setting.

There is currently a paucity of novel pharmacological mechanisms in the treatment of many psychiatric disorders, and some commentators have called for a "disruptive pharmacology" to investigate new treatments with novel mechanisms using drugs that have previously been restricted by the FDA, including psychedelic agents (146). While we support research on the medical applications of these compounds, we are realistic about the need for more clinical trials using rigorous and validated methodology in controlled settings to address concerns about the potential for substance abuse and significant medical and psychiatric sequelae in vulnerable populations. Research has been hampered by the fact that there is not a rigorous definition of psychedelic-assisted psychotherapy and the fact that the expectations and personal experiences of the study subjects are important variables in the response to psychedelic-assisted therapy (6). These variables can be difficult to account for in a clinical trial, but they should be a part of the future research agenda.

The FDA's breakthrough designation of MDMA for the treatment of PTSD and psilocybin for the treatment of depression reflects the drugs' potential to treat resistant psychiatric disorders. Recent trials have also shown that psilocybin may be effective for treating anxiety disorders, substance use disorders, and emotional suffering associated with facing the end of one's life. Clinical research data with psilocybin is particularly interesting, as it shows that several sessions of psilocybin-assisted psychotherapy can lead to antidepressant effects that persist for weeks to months. This modality of treatment might provide a therapeutic advantage over current standards of care, such as transcranial magnetic stimulation, electroconvulsive therapy, or ketamine infusion therapy, each of which requires multiple visits per week to achieve antidepressant effect and often requires multiple visits per month to sustain remission (8). While LSD and ayahuasca currently have less scientific evidence to support their use in the clinical setting, the data available at the time of this review clearly support future controlled trials to evaluate their efficacy and safety.

Of some concern is that the use of these compounds appears to be outpacing evidence-based research. The practice of microdosing LSD or psilocybin—taking low doses of psychedelics below the perceptual threshold at regular intervals (approximately once every 3–5 days) to enhance creativity, productivity, mood, or the therapeutic alliance—has become increasingly popular in recent years (4, 74, 147). The growing popularity of microdosing in the general (non–psychiatrically ill) population raises additional questions about psychedelics that might be encountered in clinical practice.

In his 1979 autobiography entitled *LSD: My Problem Child* (1), Albert Hofmann described his concerns about the potential overenthusiasm for LSD among the public: "This joy at having fathered LSD was tarnished after more than ten years of uninterrupted scientific research and medicinal use when LSD was swept up in the huge wave of an inebriant mania that began to spread over the Western world, above all the United States, at the end of the 1950s." At the time, the recreational use of LSD was increasing and had societal consequences that led to the restriction of these potentially promising psychedelic compounds from further research as treatments for psychiatric disorders. Psychedelic drugs acquired a negative reputation when they were available to the public through underground channels, without medical indication or regulation. The nascent body of data reviewed here should be leveraged to inform next-step research that asks meaningful questions about the therapeutic potential and the abuse potential of psychedelic-assisted psychotherapy in standardized clinical trials, as well as about the potential therapeutic and adverse effects of psychedelic drugs used as monotherapy.

This area of research, involving drugs with pharmacological actions different from those associated with current

TABLE 2. Recent psychedelic clinical trials[a]

Compound and Study	Design	Diagnosis	N	Dose	Placebo or Control	Psychedelic Sessions	Primary Measures	Outcome
MDMA								
Mithoefer et al. (106)	Randomized double-blind crossover	PTSD	23	125 mg, plus optional 62.5 mg	Lactose	2	CAPS	Significant reduction in PTSD symptom severity. The mean change in CAPS scores 2 months after the second experimental session was −53.7 for the MDMA group and −20.5 for the placebo group.
Mithoefer et al. (116)	Follow-up	PTSD	19	N/A	N/A	N/A	CAPS	Significant and sustained reduction in PTSD symptom severity at 74 months.
Mithoefer et al. (105)	Randomized double-blind dose-response crossover	PTSD	26	30 mg, 75 mg, or 125 mg, plus optional 1/2 initial dose	30 mg MDMA active control	2	CAPS	Significant reduction in PTSD symptom severity. The mean change in CAPS score 1 month after the second experimental session was −58.3 for the 75 mg group, −44.3 for the 125 mg group, and −11.4 for the 30 mg group.
Psilocybin								
Carhart-Harris et al. (23)	Open-label	Treatment-resistant depression	12	10 mg, and 25 mg 2 weeks later	None	2	QIDS	Significant reduction in depressive symptoms. The mean change in QIDS score was −11.8 at 1 week and −9.2 at 3 months after the experimental session.
Grob et al. (28)	Randomized double-blind placebo	Cancer-related anxiety and depression	12	0.2 mg/kg	Niacin	1	STAI, BDI	Sustained decrease in STAI scores for the entire 6-month follow-up, which reached significance at 1 and 3 months after treatment. The mean BDI score dropped by almost 30% after 1 month and reached significance at 6-month follow-up.
Griffiths et al. (18)	Randomized double-blind crossover	Cancer-related depression and anxiety	51	22 or 30 mg/70 kg	Psilocybin, 1 or 3 mg/70 kg	1	HAM-A, HAM-D	At 6-month follow-up, the overall rate of clinical response was 78% on the HAM-D and 83% on the HAM-A; the overall rate of symptom remission was 65% on the HAM-D and 57% on the HAM-A.
Ross et al. (29)	Randomized double-blind crossover	Cancer-related anxiety and depression	29	0.3 mg/kg	Niacin	1	HADS, STAI, BDI	At 6.5-month follow-up, after all participants had received psilocybin, 60%–80% of participants had clinically significant sustained reductions in depression or anxiety, sustained benefits in existential distress and quality of life, and improved attitudes toward death.
Johnson et al. (30)	Open-label	Tobacco use disorder	15	20 mg/70 kg or 30 mg/70 kg	None	2–3	Laboratory-verified abstinence	At 6-month follow-up, 80% of participants were laboratory-verified as abstinent.

continued

TABLE 2, *continued*

Compound and Study	Design	Diagnosis	N	Dose	Placebo or Control	Psychedelic Sessions	Primary Measures	Outcome
Johnson et al. (148)	Follow-up	Tobacco use disorder	15, 12	N/A	N/A	0	Laboratory-verified abstinence	At 1-year follow-up, 10/15 (67%) participants were laboratory-verified as abstinent, and at 2.5-year follow-up, 9/12 (75%) participants were laboratory-verified as abstinent.
Bogenschutz et al. (31)	Open-label	Alcohol use disorder	10	0.3 mg/kg, and 0.4 mg/kg 4 weeks later	None	2	AASE	Abstinence measured using the AASE increased significantly after psilocybin administration. Gains were largely maintained at 36-week follow-up, and the intensity of the first psilocybin session predicted changes in drinking in weeks 5–8.
LSD								
Gasser et al. (48)	Randomized double-blind crossover	Anxiety associated with life-threatening disease	12	200 μg	LSD 20 μg	2	STAI	Significant reduction in STAI state score at 2-month follow-up. The mean change in STAI state score was −11.6, and this reduction in state anxiety was sustained at 12-month follow-up.
Schmid et al. (70)	Randomized double-blind crossover	Healthy subjects	16	200 μg	Not specified	1	PEQ, MS	A moderate dose of LSD induced a subjectively meaningful experience with lasting positive effects: positive attitudes about life and/or self, positive mood changes, altruistic/positive social effects, and positive changes in well-being/life satisfaction.
Ayahuasca								
Osório et al. (87)	Open-label	Major depression with failure of one antidepressant	6	2.2 mL/kg (0.8 mg/mL DMT, 0.21 mg/mL harmine)	None	1	HAM-D, MADRS	HAM-D scores were reduced by 62% 1 day after drug administration and by 72% at 7 days. MADRS scores were reduced by 82% at 7 days, with sustained effects at 21 days.
Sanches et al. (88)	Open-label	Major depression with failure of one antidepressant	17	2.2 mL/kg (0.8 mg/mL DMT, 0.21 mg/mL harmine)	None	1	HAM-D, MADRS	Significant reductions in HAM-D and MADRS scores 1, 7, 14, and 21 days after drug administration. The mean change in HAM-D score 21 days after drug administration was −11.4.

[a] AASE=Alcohol Abstinence Self-Efficacy Scale; BDI=Beck Depression Inventory; CAPS=Clinician-Administered PTSD Scale; LSD=lysergic acid diethylamide; DMT=*N,N*-dimethyltryptamine; HADS=Hospital Anxiety and Depression Scale; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Åsberg Depression Rating Scale; MDMA=*3,4*-methylenedioxymethamphetamine; MS=Mysticism Scale; N/A=not applicable; PEQ=Persisting Effects Questionnaire; PTSD=posttraumatic stress disorder; QIDS=Quick Inventory of Depressive Symptomatology; STAI=State-Trait Anxiety Inventory.

antidepressant medications, has the potential to advance our understanding of the neurobiological processes and therapeutic outcomes achieved by patients with a variety of mood and anxiety spectrum disorders. As we have pointed out, there are significant limitations in the study methodologies, and the available evidence base includes the use of nonrepresentative samples (relative to the general population) through self-selection of individuals into clinical trials who may be biased toward expecting beneficial effects, including mystical experience related to ingestion of psychedelics; crossover study designs rather than parallel-group designs, precluding between-group comparisons for long-term follow-up outcomes with participants who received placebo; inconsistencies in medication dosing between studies; and blinding methods compromised by the pronounced effects of the

psychedelic interventions. These limitations notwithstanding, the preliminary data on the therapeutic potential of psychedelic drugs support further research.

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Psychedelic medicine: a re-emerging therapeutic paradigm

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In clinical research settings around the world, renewed investigations are taking place on the use of psychedelic substances for treating illnesses such as addiction, depression, anxiety and posttraumatic stress disorder (PTSD). Since the termination of a period of research from the 1950s to the early 1970s, most psychedelic substances have been classified as "drugs of abuse" with no recognized medical value. However, controlled clinical studies have recently been conducted to assess the basic psychopharmacological properties and therapeutic efficacy of these drugs as adjuncts to existing psychotherapeutic approaches. Central to this revival is the re-emergence of a paradigm that acknowledges the importance of set (i.e., psychological expectations), setting (i.e., physical environment) and the therapeutic clinician–patient relationship as critical elements for facilitating healing experiences and realizing positive outcomes.[1,2]

The public is often well-versed in the potential harms of psychedelic drugs, but much of this knowledge is from cases involving patients who used illicit substances in unsupervised nonmedical contexts. We discuss the emerging research for therapeutic purposes involving human subjects, considering both the possible benefits and the potential harms of using psychedelic agents as adjuncts to psychotherapy or counselling for mental illness.

Types of psychedelic drugs

"Psychedelic" drugs include a range of substances with varying pharmacological profiles that all have strong effects on conscious experience (Table 1).[3–18] We will focus on two classes of psychedelics: classic psychedelics and "entactogens."

The classic psychedelics exert primary activity as agonists at the 5-HT_{2A} receptor (e.g., lysergic acid diethylamide [LSD], psilocybin, dimethyltryptamine [DMT] and mescaline).[19] Many of these substances are found — or are close analogues of chemicals found — in plants or fungi used traditionally for millennia in spiritual or folk healing rituals, such as the ergot fungus (*Claviceps purpurea*) from Eurasia, morning glory (*Turbina corymbosa*) and peyote cactus (*Lophophora williamsii*) from Central and North America, and the ayahuasca brew (*Banisteriopsis caapi* and *Psychotria viridis*) from the Amazon.[20]

The second class of psychedelic substances, the entactogens, includes methylenedioxymethamphetamine (MDMA), which acts primarily as a serotonin-releasing agent and has effects that somewhat overlap but are substantially distinct from classic psychedelics.[21]

Other substances that are sometimes classified as "psychedelic" — such as ketamine (a dissociative anesthetic), scopolamine (an anticholinergic) or ibogaine (a substance with a complex neuropharmacology) — are beyond the scope of this review. This article will focus on clinically relevant studies with patient populations in which psychedelic drugs are used as adjuncts to psychotherapy. Besides a few brief mentions, we do not cover findings from research on healthy participants, although such studies have been the basis of renewed neuropharmacologic science in this field.

Key points

- Medical interest in psychedelic drugs as treatments for illnesses such as anxiety, addiction and posttraumatic stress disorder has been renewed.
- Small-scale studies involving human participants in the United States, Europe and Canada are showing that such research can be conducted in a safe and scientifically rigorous manner.
- Preliminary findings show some successful results for these treatments, with significant clinical improvements and few — if any — serious adverse effects.
- The emerging results may have implications for future medical and neuroscientific research, medical education and training, and public policy.

Contexts and indications

Some of the mental disorders for which psychedelic-assisted treatments are currently being researched include anxiety, addiction and PTSD. The findings presented in this analysis are preliminary, and most are results from small-scale pilot studies with relatively few participants. Further study is warranted before any unambiguous clinical utility may be confirmed, but the new generation of investigators is attempting to over-

come some of the methodological weaknesses of earlier research on these substances.

Anxiety

In 2014, a small randomized controlled trial in Switzerland suggested LSD-assisted psychotherapy had the potential to reduce the anxiety associated with terminal illness.[4] Twelve participants with life-threatening illness were enrolled in the study to receive treatment that involved drug-free psychotherapy sessions supplemented with two LSD-assisted sessions two to three weeks apart. The participants were randomly assigned to either the treatment group (receiving 200 μg LSD [n = 8]) or the active control group (20 μg LSD [n = 4], with an open-label crossover to 200 μg LSD after the initial blinding was unmasked). At two months' follow-up, the State–Trait Anxiety Inventory (STAI) showed nonsignificant reductions in

Table 1: Psychedelic agents currently under investigation for their potential benefits as adjuncts to psychotherapy

Substance	Derivation or chemical analogues	General effects and properties	Potential harms*	Potential therapeutic uses†
LSD	Ergot fungus (*Claviceps purpurea*); morning glory (*Turbina corymbosa*); Hawaiian baby woodrose (*Argyreia nervosa*) — sources of ergine or lysergic acid amide	• 5-HT_{2A} (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Hallucinogen persisting perception disorder	• Addiction (e.g., alcohol)[3] • Anxiety associated with terminal illness[4,5]
Psilocybin	Psilocybe and other genera of mushrooms (various species)	• 5-HT_{2A} (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Hallucinogen persisting perception disorder	• Addiction (tobacco, alcohol)[6,7] • Anxiety associated with terminal illness[8]
Ayahuasca brew (admixtures contain DMT)	Chacruna leaf (*Psychotria viridis*); Chagropanga vine (*Diplopterys cabrerana*); ayahuasca vine (*Banisteriopsis caapi*); assorted other admixture plants	• 5-HT_{2A} (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Nausea, emesis • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis • Serotonin syndrome and other dangers from medication interactions due to monoamine oxidase inhibitory activity	• Addiction (alcohol, cocaine, tobacco)[9,10] • Depression, anxiety[11–14]
Mescaline	Peyote cactus (*Lophophora williamsii*); San Pedro cactus (*Echinopsis pachanoi*)	• 5-HT_{2A} (serotonin) agonist of pyramidal neurons • Dizziness, weakness, tremors, paresthesia • Altered consciousness (visions, auditory distortions, ideations) • Altered mood (happy, sad, fearful, irritable) • Distorted sense of space, time	• Psychosis	• Addiction (alcohol)[15]
MDMA	Sassafras tree (*Sassafras albidum*) — source of safrole, precursor chemical	• Serotonin, dopamine and noradrenaline agonist • Euphoria • Arousal • Perceptual alteration • Enhanced empathy and sociability	• Potential neurocognitive deficits (e.g., memory impairment) • Sleep disruption • Short-term depression	• PTSD[16–18]

Note: DMT = dimethyltryptamine, LSD = lysergic acid diethylamide, MDMA = methylenedioxymethamphetamine, PTSD = posttraumatic stress disorder.
*Potential harms identified here are associated with illicit and unsupervised nonmedical uses of psychedelic substances (often in the context of polysubstance use); current clinical studies on psychedelic agents have not reported such chronic adverse sequelae.
†Potential therapeutic uses are identified based on evidence from past (i.e., 1950s–1960s) and current research on psychedelic drugs.

trait anxiety, but significant reductions in state anxiety.

Follow-up with nine participants one year after treatment showed a sustained therapeutic benefit with no acute or chronic drug-related severe adverse events, and there were no adverse effects lasting more than one day after an LSD-assisted session.[4]

Psilocybin has likewise shown promise as a treatment for anxiety in patients with terminal illness.[8] A 2008 study on ameliorating end-of-life anxiety focused on 12 participants with end-stage cancer.[8] After several non–drug-assisted therapy sessions, participants underwent a within-subject crossover study in which they received the experimental medication (0.2 mg/kg psilocybin) and the active placebo (250 mg of niacin) across two sessions a few weeks apart. Findings showed that psilocybin-assisted psychotherapy lowered anxiety and improved mood, without clinically significant adverse effects.[8]

MDMA-assisted therapy is also being studied as a treatment for social anxiety in adults with autism, although findings have yet to be published.[22]

Addiction

Researchers in the 1950s and 1960s studied the use of psychedelic-assisted therapy for the treatment of addictions such as alcohol dependence,[23] some key findings of which were recently reviewed in a meta-analysis that suggested a significant beneficial effect.[3] In renewed clinical research on treating alcohol dependence with psilocybin-assisted therapy, a New Mexico team recruited 10 participants with a diagnosis of active alcohol dependence (and no concurrent mental illness or other substance use disorder).[6] Participants received pre- and post-psychosocial support (motivational enhancement therapy) over 12 weeks, with one or two intervening open-label sessions at weeks four (0.3 mg/kg psilocybin, $n = 10$) and eight (0.4 mg/kg psilocybin, $n = 6$, or 0.3 mg/kg psilocybin, $n = 1$). Among the participants who completed the study, the self-reported mean percent drinking days and percent heavy drinking days were reduced by more than half of what had been reported at baseline.[6] Acute adverse effects such as nausea and mild headaches were reported by some participants, but no clinically significant or lasting harms resulted from the administration of psilocybin.

Other recent research on psilocybin-assisted psychotherapy for addiction includes a pilot study of treatment for tobacco dependence. This investigation was an open-label design involving 15 participants who smoked at least 10 cigarettes per day and had multiple previous unsuccessful cessation attempts.[7] Participants received cognitive behavioural therapy before and after treatment with psilocybin. Treatment included two or three psilocybin-assisted psychotherapy sessions (doses of either 20 mg/70 kg or 30 mg/70 kg), with the first session occurring on the target quit date. At six months' follow-up, 12 of the 15 participants were abstinent (biologically verified by exhaled carbon monoxide and urinary cotinine levels).[7] Smoking cessation outcomes were significantly correlated with a measure of mystical experience on session days, as well as retrospective ratings of personal meaning and spiritual significance of psilocybin sessions.[24] The same research team is currently designing a follow-up randomized controlled study to compare a similar psilocybin intervention with nicotine-replacement therapy.

The Amazonian folk medicine ayahuasca is a plant-based preparation with the psychoactive constituents DMT, which is chemically related to psilocybin, and harmala alkaloids, which are reversible monoamine oxidase inhibitors. An observational study of an ayahuasca-assisted intervention in a Coast Salish First Nations community in British Columbia for people ($n = 12$) seeking treatment for addictions to substances such as alcohol and cocaine showed statistically significant improvements in measures of mental health and reductions in self-reported use of these substances after six months, with no lasting adverse physical or psychological effects.[9]

Observational research involving members of Brazilian religious groups who regularly drink ayahuasca sacramentally has shown that, compared with a matched control group, long-term regular drinkers of ayahuasca tend to have a lower prevalence of substance use,[10] structural brain changes that do not suggest evident pathology[11] and better neuropsychological performance and psychosocial adaptation.[12] Other studies involving similar populations of long-term drinkers of ayahuasca have shown lower rates of psychoactive substance use and psychopathology.[13,14]

Canadian researchers are currently coordinating an international research study to investigate ayahuasca's potential as a treatment for addiction, with clinical sites in Brazil, Peru and Mexico.[25]

Ayahuasca differs from the other substances covered in this review, inasmuch as it is a plant-based preparation of variable composition and strength, and typically used in ceremonial contexts, which makes it more difficult for researchers to isolate the factors that may contribute to therapeutic efficacy.[26,27]

Posttraumatic stress disorder

In a pilot randomized controlled trial investigating MDMA-assisted psychotherapy to treat chronic treatment-resistant PTSD in the United States, outcomes from 20 participants with a mean illness

duration of 19 years showed that the experimental treatment may improve upon the best currently available pharmacotherapies and psychotherapies.[16] The clinical protocol involved several weeks of preparatory and follow-up non–drug-assisted psychotherapy, during which the members of the experimental group received two MDMA-assisted sessions. No serious adverse effects were reported. Outcomes included a significant and sustained reduction in PTSD symptoms as measured by the Clinician-Administered PTSD Scale (CAPS), with 83% of participants in the experimental group (v. 25% in the placebo group) showing a reduction in symptom severity of more than 30%. Furthermore, some members of the experimental group no longer met criteria for PTSD as stated in the *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition* (DSM-IV).[16] A long-term follow-up study involving the same participants showed that, although two patients relapsed, 74% (14/19) of patients still showed meaningful, sustained reductions in their CAPS scores three and a half years later.[17]

An additional small (n = 12) randomized controlled trial investigating MDMA-assisted psychotherapy for PTSD was recently completed in Switzerland.[18] This study compared three full-dose MDMA-assisted sessions per patient (with non–drug-assisted therapy before and after) with low-dose active placebo in a crossover design. Participants had no serious drug-related adverse events, and although reductions in CAPS scores were not statistically significant, self-assessment of PTSD symptoms as measured by the Posttraumatic Diagnostic Scale questionnaire was significantly reduced.

In 2015, researchers in Vancouver began a similar pilot study of MDMA-assisted psychotherapy for patients with PTSD, the first clinical study involving psychedelic drugs in Canada in more than 40 years.

Historical lessons

Experience from previous research — both positive and negative — has provided important lessons for current methodological designs, ethical strictures and clinical protocols and for renewed research on psychedelics involving human participants. In the 1950s and 1960s, methodological challenges confounded the advancement of psychedelic medicine, with researchers disagreeing about the suitability of randomized controlled trials and the possibility of double-blinding.[28] More infamously, egregious violations of ethical protocols, such as lack of informed consent (in some cases through military or intelligence agency–supported research) resulted in substantial and long-lasting harms to some patients.[23] Furthermore, unsupported claims about purported benefits of psychedelics, and sometimes explicit encouragement for non-clinical use, by some members of the research community, may have contributed to unsupervised and uncontrolled recreational use of psychedelic substances. Consequently, by the mid-1970s, clinical access to and professional interest in psychedelic drugs waned, leading to a quiescence in research for several decades.

Although methodological and political challenges remain to some degree,[27] recent clinical studies have shown that studies on psychedelics as therapeutic agents can conform to the rigorous scientific, ethical and safety standards expected of contemporary medical research.[29] For example, patients undergo careful screening, fully informed consent is obtained and protocols are approved by ethics review boards. In addition, contemporary investigators are mindful of the checkered history of psychedelic research, and are thus cautiously reserved in reporting their findings, doing so with appropriate caveats and limitations.

Potential risks and their mitigation

Most psychedelic drugs are classified and legally scheduled as having no or very limited medical purpose, a high potential for abuse and a lack of accepted safety for use under medical supervision.[30] Potential health risks of these substances include the precipitation of psychotic breaks in patients with psychotic disorders or a predisposition to these disorders.[31] Thus, participation in contemporary psychedelic research typically excludes people with a personal or family history of psychosis or bipolar disorder.[29]

A further risk associated with psychedelic drugs is Hallucinogen Persisting Perception Disorder (HPPD), sometimes known as "flashbacks," although HPPD is more uncommon and more clinically severe than the flashbacks or visual distortions sometimes described in the days following illicit use of psychedelics.[32,33] However, the incidence of adverse effects such as psychosis or HPPD in the general population is believed to be relatively low, and these effects are generally associated with the use of illicitly procured psychedelic substances, which often involves polysubstance use in uncontrolled settings without supervision.[34] In light of these concerns, it is worth noting that lifetime use of classic psychedelics at the population level is associated with decreased psychological distress;[35] thus, potential individual instances of harm may be overshadowed by instances in which people experience benefit or no harm.

The most common adverse effects from the administration of psychedelics under clinical supervision are limited to the time of drug action, such as acute increases in anxiety, fear, heart rate and blood pressure.[29] Without careful supervision, fearful responses could lead to dangerous behaviour (e.g., fleeing the study site). In addition, delayed-onset headache is sometimes caused by psilocybin use and possibly by other classic psychedelics.[36] Although adverse effects of MDMA overlap somewhat with those of classic psychedelics, cardiovascular effects (e.g., tachycardia) are generally greater with MDMA, whereas adverse psychological reactions are more likely with classic psychedelics. It is important to note that acute adverse effects are readily managed,[37] and that, as described previously, none of the new clinical research studies have reported long-term harms.

The clinical protocols for contemporary psychedelic studies draw on lessons learned from the earlier era of psychedelic research, and incorporate some common elements to minimize risks and maximize potential therapeutic benefit. After obtaining fully informed consent from the patient, clinical sessions take place in health care facilities, in quiet treatment rooms with pleasant and comfortable decor. Headphones deliver music, hospital and laboratory equipment are minimal and discreetly placed, and a two-person cotherapist team is in attendance throughout the drug's action. During a session, interaction between patient and therapists is kept to a minimum, with the patient encouraged to spend much of the time engaging in self-reflection while listening to carefully selected music. Follow-up sessions that are non-drug assisted provide opportunities to integrate the insights gleaned from the experimental sessions. As research on psychedelic medicine advances, further refinements in screening, safety and therapeutic protocols will be possible.

Questions for future research

Numerous scientific and empirical questions remain in the field of psychedelic medicine. With respect to basic neuroscience research, progress in understanding the human brain and its functional relationship to mind and consciousness would be substantially advanced by further determining how psychedelic drugs work neuropharmacologically.[30] This kind of knowledge would in turn be useful in applied fields such as psychology, psychiatry and addiction medicine, both to help explain mechanisms for the therapeutic results that renewed psychedelic studies are yielding and to advance understanding about optimal therapeutic protocols for these forms of treatment. With respect to clinical applications, different psychedelic medications may be indicated for different specific illnesses. Further research should elucidate not only respective efficacy, but also optimal pharmacotherapeutic and ancillary psychotherapeutic choices.

Beyond basic research on neuropharmacological mechanisms and clinical outcomes are potential economic arguments for psychedelic therapies. Substance dependence and mental disorders, such as depression and anxiety, are substantial and growing sources of illness and health system costs worldwide.[38,39] Given these trends, investment of resources into researching novel treatments for mental and substance use disorders is warranted. Because preliminary evidence suggests psychedelic therapies require relatively time-limited interventions (i.e., they do not involve long-term ongoing courses of pharmacotherapeutic intervention), they may prove to be economically viable in comparison with currently available treatments.

Conclusion

Renewed scientific interest in psychedelic medicine is generating new knowledge about a class of pharmacologic substances that humans have long used for ceremonial, therapeutic and cultural purposes. As this field of research evolves, medical school curricula may need to be updated to include the latest knowledge about psychedelic drugs. This would encompass scientific evidence about relative risks and harms of psychedelic drugs — which is largely absent in current drug control scheduling classifications[40] and reflects adverse outcomes from uncontrolled recreational use rather than supervised clinical settings. In addition, it would encompass knowledge about the potential therapeutic uses of these agents, particularly because patients may query their physicians about research findings reported in the media. If further scientific evidence accumulates on the therapeutic value of psychedelic medicines, specialized clinical training for physicians, nurses, psychologists and other health professionals will be required to meet an increased demand for such treatments.

It behooves policy-makers to be aware of and open to new approaches to treatments emerging in the field of psychedelic medicine. This is particularly important for those concerned about the growing prevalence of mental illness, including addiction, as well as its associated human, social and economic costs. This applies not only to elected officials, but also to civil servants in health ministries and research granting agencies, where advances and innovations are translated from the clinical research laboratory into options for health care improvements that are in the public interest. Currently, international drug control scheduling classifications and popular miscon-

ceptions about the relative risks and harms of psychedelic drugs make research involving humans difficult. However, continued medical research and scientific inquiry into psychedelic drugs may offer new ways to treat mental illness and addiction in patients who do not benefit from currently available treatments. The re-emerging paradigm of psychedelic medicine may open clinical and therapeutic doors long closed.

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Original Article

Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer

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Abstract

Background: A recently published randomized controlled trial compared single-dose psilocybin with single-dose niacin in conjunction with psychotherapy in participants with cancer-related psychiatric distress. Results suggested that psilocybin-assisted psychotherapy facilitated improvements in psychiatric and existential distress, quality of life, and spiritual well-being up to seven weeks prior to the crossover. At the 6.5-month follow-up, after the crossover, 60–80% of participants continued to meet criteria for clinically significant antidepressant or anxiolytic responses.

Methods: The present study is a long-term within-subjects follow-up analysis of self-reported symptomatology involving a subset of participants that completed the parent trial. All 16 participants who were still alive were contacted, and 15 participants agreed to participate at an average of 3.2 and 4.5 years following psilocybin administration.

Results: Reductions in anxiety, depression, hopelessness, demoralization, and death anxiety were sustained at the first and second follow-ups. Within-group effect sizes were large. At the second (4.5 year) follow-up approximately 60–80% of participants met criteria for clinically significant antidepressant or anxiolytic responses. Participants overwhelmingly (71–100%) attributed positive life changes to the psilocybin-assisted therapy experience and rated it among the most personally meaningful and spiritually significant experiences of their lives.

Conclusion: These findings suggest that psilocybin-assisted psychotherapy holds promise in promoting long-term relief from cancer-related psychiatric distress. Limited conclusions, however, can be drawn regarding the efficacy of this therapy due to the crossover design of the parent study. Nonetheless, the present study adds to the emerging literature base suggesting that psilocybin-facilitated therapy may enhance the psychological, emotional, and spiritual well-being of patients with life-threatening cancer.

Keywords
Psilocybin, psychedelic, cancer, depression, anxiety

Introduction

Cancer is a leading cause of morbidity and mortality globally, with approximately 14 m new diagnoses made annually (Ferlay et al., 2013). Despite technological advancements that have led to earlier detection and significantly improved medical treatments for cancer, the diagnosis still provokes intense fear and distress among many patients (Lee, 2008). It is common for cancer patients to develop psychiatric distress with rates of anxiety and depressive disorders as high as 40% in hospital settings (Mitchell et al., 2011). Medical providers often neglect or inadequately address these symptoms (Gouveia et al., 2015). Clinically significant depression and anxiety among cancer patients are associated with several poor outcomes including decreased quality of life and cancer survival rates, reduced treatment adherence, and increased desire for death and rates of suicide (Amiri and Behnezhad, 2019; Jaiswal et al., 2014).

Psycho-oncology is increasingly recognizing the unique existential challenges accompanying a cancer diagnosis (Breitbart et al., 2000). Existential distress has been described as mental distress experienced by those facing imminent death and associated with demoralization, absence of purpose or meaning, hopelessness, isolation, and loss of dignity (Kissane, 2000; Murata, 2003). Psychotropic medications are commonly used to treat cancer-related distress, but evidence supporting efficacy is limited and inconsistent (Grassi et al., 2014; National Comprehensive Cancer Network, 2014), and significant side effects have been found to adversely affect treatment compliance

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(Li et al., 2012). Several meta-analyses of placebo-controlled trials of antidepressants have failed to demonstrate a clear effect of treatment over placebo in cancer patients (Iovieno et al., 2011; Laoutidis and Mathiak, 2013; Ostuzzi et al., 2015). Psychosocial interventions have been developed to specifically target the existential and spiritual distress of cancer patients, albeit with limited efficacy (Chochinov et al., 2011; LeMay and Wilson, 2008) and relatively weak methodological study designs (Xing et al., 2018). There is a compelling need to develop more rigorous, well-designed trials that adequately assess the efficacy of existing spiritual and existential interventions. There is also a need to develop novel interventions that can increase the effect sizes of interventions aimed at improving the psychospiritual states of people with cancer.

In response to the limited evidence supporting the efficacy of existing approaches to treating psychiatric and existential distress, researchers have deployed attention toward examining the therapeutic potential of serotonergic psychedelics (Reiche et al., 2018). Historically, classic psychedelics were studied as novel therapeutic agents in the psychiatric treatment of patients with cancer. In the 1950s and 1960s researchers funded by the National Institute of Mental Health (NIMH) conducted trials with hundreds of participants and found that psychedelics such as d-lysergic acid diethylamide (LSD) alleviated depression, anxiety, and pain, and improved sleep and quality of life associated with cancer (Kast, 1970; Kast and Collins, 1964; Grof et al., 1973). After a quiescence of over two decades, clinical trials with the classical psychedelics resumed. Four recently published crossover randomized controlled trials (RCTs) administered psilocybin (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016) and LSD (Gasser et al., 2014; 2015) with psychological support to participants with cancer diagnoses or life-threatening illnesses (N=104) and established overall safety and preliminary efficacy with medium to large effects. Despite the promising evidence regarding the acute therapeutic effects of psychedelics, there is a modest amount of data suggesting safety and efficacy of these interventions in the long-term. The longest follow-up in these studies occured at 12 months post-crossover in one of these trials, at which time significant reductions in anxiety were sustained following two doses of LSD combined with psychotherapy (Gasser et al., 2015).

The present study is a long-term follow-up (LTFU) analysis of a randomized placebo-controlled trial that compared a single dose of psilocybin (0.3 mg/kg) with a single dose of niacin (250 mg) in conjunction with psychotherapy in patients (N=29) with cancer-related psychiatric and existential distress (Ross et al., 2016). In the parent trial, results suggested that psilocybin-assisted psychotherapy catalyzed rapid antidepressant and anxiolytic effects with large effect sizes and rates of clinical response up to seven weeks (prior to study crossover). After the crossover at the final (6.5-month) point, approximately 60–80% of patients met the criteria for clinically significant antidepressant or anxiolytic responses. Psilocybin also appeared to yield acute and sustained reductions in demoralization and hopelessness, as well as improvements in spiritual well-being and quality of life. There were no significant improvements in death anxiety. Seventy percent of participants rated the experience as the single or top-five most personally meaningful experience(s) of their lives, and 52% rated it the single or top-five most spiritually significant experience(s) of their lives. Ratings of mystical-type experiences were found to partially mediate the effect of psilocybin versus placebo on anxiety and depression outcomes (Ross et al., 2016). Limited conclusions, however, can be drawn regarding the efficacy of psilocybin-assisted therapy beyond the seven-week point due to the crossover design. The objective of the present study was to determine whether benefits reported at parent study completion were maintained at two extended LTFU points.

Methods

The NYU School of Medicine Institutional Review Board approved a protocol amendment for the addition of the LTFU data collection. Participants in this present study had previously concluded treatment in our parent study (for full details of this study see Ross et al., 2016). Of the original 29 participants, we contacted all 16 participants who were not deceased at the time of LTFU (the remaining 13 participants were deceased). All of these participants had agreed to be contacted about future research opportunities. Of the 16 participants who were contacted, 15 agreed to participate in the LTFU and completed measures through a secure online portal. One participant died (from cancer-related complications) after completing the first LTFU and prior to the second LTFU, leaving us with 14 participants at the second LTFU. The first and second LTFUs occurred on average 3.2 years (range 2.3–4.5 years) and 4.5 years (range 3.5–5.5 years) following the participants' psilocybin dosing date, respectively.

In the parent study, participants were randomly assigned to one of two groups: psilocybin (0.3 mg/kg) on the first medication session followed by niacin (250 mg) on the second session (i.e. psilocybin-first group), or niacin (250 mg) on the first medication session followed by psilocybin (0.3 mg/kg) on the second session (i.e. niacin-first group). Participants received nine total preparatory psychotherapy sessions and post-medication integration sessions delivered by a dyadic therapy team. The trial employed a crossover design at seven weeks following the first drug administration, with the final outcome assessment at 6.5 months following the second drug administration (i.e. after the crossover).

Participants

Demographic information is presented in Table 1. At the first LTFU, the mean age of participants was 53 years old (standard deviation (SD)=16 years), and they were predominantly female (60%). The majority was non-Hispanic White (93%), followed by Asian (6%). Forty percent reported Catholic/Christian or Jewish beliefs, and one-third (33%) reported atheist/agnostic beliefs, followed by "other" faith/tradition (13%). Gynecological cancers (33%) comprised the majority of disease sites, followed by breast (20%) and lymphomas (20%). Slightly more than half (60%) were diagnosed with early stage (I–II) cancers versus later stage (III–IV; 53%) at the parent study end point. Of note, at the second LTFU, 71% of participants had reportedly entered partial or complete remission from their cancers, and 29% were in the active stages of their diseases. Approximately half (53%) of all participants reported one or more occasions of prior hallucinogen use. The majority of participants (93%) met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) criteria for cancer-related adjustment disorder with anxious and/or depressed features, followed by generalized anxiety disorder (7%). Compared to the parent study sample (Ross et al., 2016), the proportions of current study participants were roughly

Table 1. Demographic and clinical characteristics of study participants at LTFU follow-ups.

Characteristic	Categories	Total	
		N=15	
Sex	Female	9	60.00%
	Male	6	40.00%
Age at follow-up; mean (SD)	Range 25–73	53 (15.5)	
Race	White/Caucasian	14	93.33%
	Asian	1	6.67%
Religious/ spiritual beliefs	Atheist/agnostic	5	33.33%
	Jewish	3	20.00%
	Catholic	1	6.67%
	Other Christian	2	13.33%
	Other faith/tradition	2	13.33%
Site of cancer	Breast	3	20.00%
	Reproductive	5	33.32%
	Lymphoma/leukemia	3	20.00%
	Other types	4	26.67%
Stage of cancer	Stage IV	2	13.33%
	Stage III	4	26.67%
	Stage II	3	20.00%
	Stage I	5	33.32%
	Other	1	6.67%
SCID (DSM-IV-TR) diagnosis	Adjustment disorder w/ anxiety and depressed mood, chronic	2	13.33%
	Adjustment disorder w/ anxiety, chronic	12	80.00%
	Generalized anxiety disorder	1	6.67%
Hallucinogen use	No	8	53.33%
	Yes	7	46.67%
Education	Part-college	2	13.33%
	Graduated 4-year college	4	26.67%
	Completed grad/professional school	9	60.00%

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders; SD: standard deviation; SCID: Structured Clinical Interview for DSM Disorders.

equivalent in all demographic variables with the exception of cancer type. There was a greater proportion of reproductive cancer in this LTFU sample than in the parent sample, and no participants carried a diagnosis of digestive cancers in the LTFU sample (compared to 21% in the parent sample).

Psychiatric interventions received during follow-up period and adverse events

A total of 13 out of the 14 participants who completed the second LTFU time point provided information regarding their use of psychotherapy or pharmacological interventions after completion of the parent study. One participant who participated in the LTFU passed away prior to the administration of this assessment. Participants provided the name, dosage, duration, and reason for medication prescription, as well as type, duration, and reason for any psychotherapy intervention received during the LTFU period. Eight participants (53%) reported taking medication daily for anxiety or depression at study screening but discontinued prior to enrollment due to the parent study exclusion criteria. Participants were allowed to take prescribed Benzodiazepines on an as needed basis up to three days prior to their first medication session. During the LTFU period five participants reported (39%) receiving some form of psychotherapy since completion of the parent trial, with one (8%) receiving psychotherapy specifically targeting cancer-related psychological distress. Three participants (23%) received some form of psychotropic drug treatment, with no participants receiving psychotropic medication specifically targeting cancer-related psychological distress during the LTFU period. None of the participants reported lasting negative or adverse effects from the psilocybin-assisted therapy experiences.

Measures

In the parent trial, primary measures were administered at the following time points: baseline, one day before and one day after the first and second drug administrations, two weeks and six weeks after the first and second drug administrations, and 26 weeks (6.5 months) after the second drug administration. Secondary measures were administered at baseline, two weeks and six weeks after the first and second drug administrations, and 26 weeks (6.5 months) after the second drug administration. The following measures were re-administered to participants at the two LTFU points in the present study.

Primary measures

Anxiety and depression measures. The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) is widely used in hospital settings to screen for the severity of anxiety and depression. It contains 14 questions rated on a four-point scale (total score (HAD-T) ranges from 0–56). Subscale scores can be calculated for depression (HADS-D) and anxiety (HADS-A). Although there is no single accepted cut-off score, the instrument's authors suggest that subscale scores equal to or above eight and full-scale scores over 12 indicate the possible presence of a clinical disorder (Snaith and Zigmond, 1994). The HADS has shown good reliability (Cronbach's α ranging from 0.80–0.93) and has been well validated (Herrmann, 1997).

The Beck Depression Inventory-II (BDI-II; Beck et al., 1988) is a widely used self-report screening measure for depression. The BDI-II consists of 21 questions about depressive symptoms experienced over the past two weeks rated on a three-point scale (total score ranges from 0–63). Scores above 12 indicate possible clinical depression. This measure has shown good reliability (internal consistency of 0.90) and factorial validity (Storch et al. 2004).

The State-Trait Anxiety Inventory (STAI; Spielberger, 1983) is a well-known measure of anxiety consisting of scales for state (STAI-S) and trait-level anxiety (STAI-T). Each scale contains 20 items rated on a four-point scale (subscale scores ranging from 20–80). Scores above 40 on each subscale indicate clinical presence of anxiety symptoms. The measure has shown good reliability (Cronbach's α ranging from 0.83–0.86) and discriminant validity (Quek et al., 2004).

Secondary measures

Existential distress. The Death Anxiety Scale (DAS; Templer, 1970) is a 15-item measure that has been used most frequently to assess death anxiety. Items are scored "true" and "false" and then scored as one and zero, respectively. Total scores range between 0–15. Higher scores represent increased severity of death anxiety. Scores below eight are considered normative levels of death anxiety. Templer (1970) reported adequate test-retest reliability (r=0.83) and validity.

The Hopelessness Assessment in Illness (HAI; Rosenfeld et al., 2011) is an eight-item instrument developed for use in patients with advanced cancer. Total scores range from 0–16. Higher scores indicate higher levels of hopelessness. Data have not been published regarding recommended clinical cutoff scores for this measure. This measure has shown adequate internal consistency (Cronbach's α=0.87) and concurrent validity (r=0.70–0.78; Rosenfeld et al., 2011).

The Demoralization Scale (DS; Kissane et al., 2004) is a 24-item questionnaire measuring existential distress encompassing five factors. These dimensions include loss of meaning, despair, disheartened feelings, helpless feelings, and a sense of failure. Likert scale items range from 0–4, and total scores range from 0–96. Score above 30 are considered indicative of clinical levels of demoralization. This measure has shown good reliability (Cronbach's α ranging from 0.71–0.89) and concurrent validity, with regard to related scales (Kissane et al. 2004).

Quality of life. The World Health Organization Quality of Life-Brief Version (WHOQOL-BREF; World Health Organization, 1994) is a 26-item measure providing a broad measure of quality of life across four domains: physical health, psychological health, social relationships, and environment. Likert scale items range from 1–5, and total scores from each of the four domains range from 4–20. There are no published cutoff scores above which quality of life may be considered adequate. This measure has shown good reliability (Cronbach's α ranging from 0.68–0.85) and has been well validated (Oliveira et al. 2016).

Spirituality. The Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-Sp-12; Bredle et al., 2011) is a 12-item measure of spiritual well-being among individuals with cancer and other forms of chronic illness. Items are rated on a five-point Likert scale. The measure yields three subscales: a sense of meaning/peace in life, a sense of comfort from one's faith, and total spiritual well-being score. Total scores for each subscale range from 0–32, 0–16, and 0–48, respectively. Data have not been published regarding recommended cutoff scores for this measure. This measure has shown good reliability (Cronbach's α ranging from 0.81–0.88) and has been well validated (Bredle et al. 2011).

Persisting effects of psilocybin. The Persisting Effects Questionnaire (Griffiths et al., 2006, 2008) assesses self-rated changes in one's attitude, mood, behavior, and experience of spirituality. This measure can detect longitudinal effects of psilocybin administration. An 89-item version was administered to participants in the parent study. In the present LTFU study, the following four questions were drawn from the original version. Participants were asked to indicate: (a) the personal meaningfulness of the psilocybin experience (rated from 1–8, with 1=no more than routine every-day experiences; 7=among the five most meaningful experiences of my life; and 8=the single most meaningful experience of my life); (b) the degree to which the experience was spiritually significant (rated from 1–6, 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); (c) whether the experience and their contemplation of that experience led to changes in their current sense of personal well-being or life satisfaction (rated from +3=increased very much; +2=increased moderately; +1=increased slightly, 0=no change, −1=decreased slightly, −2=decreased moderately, and −3=decreased very much; (d) and the degree to which their behaviors have changed positively as a result of the experience (rated from 0=none, 1=so slight cannot decide, 2=slight, 3=moderate, 4=strong, and 5=extreme).

Mystical experience. Mystical Experience Questionnaire (MEQ-30; MacLean et al., 2012) is a 30-item self-report questionnaire that measures qualities of mystical-type experiences occasioned by a psychedelic. The scale comprises four subscales: "Mystical" factor, "Transcendence of time and space," "Positive mood," and "Ineffability." Items are measured on a six-point Likert scale ranging from zero (not at all) to six (extremely, more than any other time in my life). Total scores range from 30–180. This measure has shown good reliability (Cronbach's α ranging from 0.80–0.93) and has been well validated (MacLean et al. 2012).

Data analysis

Regarding all analyses for both the primary and secondary outcome assessments, both the psilocybin-first and niacin-first dose sequence groups were collapsed and combined into one group. Reasons for this decision included the crossover design, which prevented valid between-group comparisons subsequent to the crossover, and a need to increase power given the modest sample size. The long-terms effects of psilocybin on variables of interest were evaluated using four repeated measures regressions, estimated within the mixed effect repeated measurement (MMRM) model. Planned within-subject t-tests (Tukey's post-hoc) were conducted comparing scores at baseline to the following time points for primary and secondary outcomes: 6.5 months after the second medication session, and the first and second LTFU points. Planned within-subject t-tests were also conducted comparing scores at parent study endpoint (6.5 months) to the two LTFU points. Remissions status (partial or complete remission versus an active diagnosis of cancer) was entered as a covariate into the MMRM model to examine whether it significantly impacted symptomatology on primary and secondary outcome measures.

Rates of clinically significant responses and symptom remission were calculated for primary outcome measures that have empirical support in defining antidepressant (HADS-D, BDI) or anxiolytic response (HADS-A) for each of the dose-sequence groups. Clinical significance was defined as 50% or greater reduction in a score at a particular assessment point relative to baseline (Rush et al., 2006). Antidepressant symptom remission was defined as 50% or greater reduction in depressive symptoms in addition to HADS-D⩽7 (Hung et al., 2012) or BDI⩽12 (Reeves et al., 2012; Riedel et al., 2010).

Participants were asked to reflect on their psilocybin session and to rate persisting effects attributed to the medication sessions on four items on the Persisting Effects Questinnaire at the second LTFU: positive behavioral change, meaningfulness, spiritual

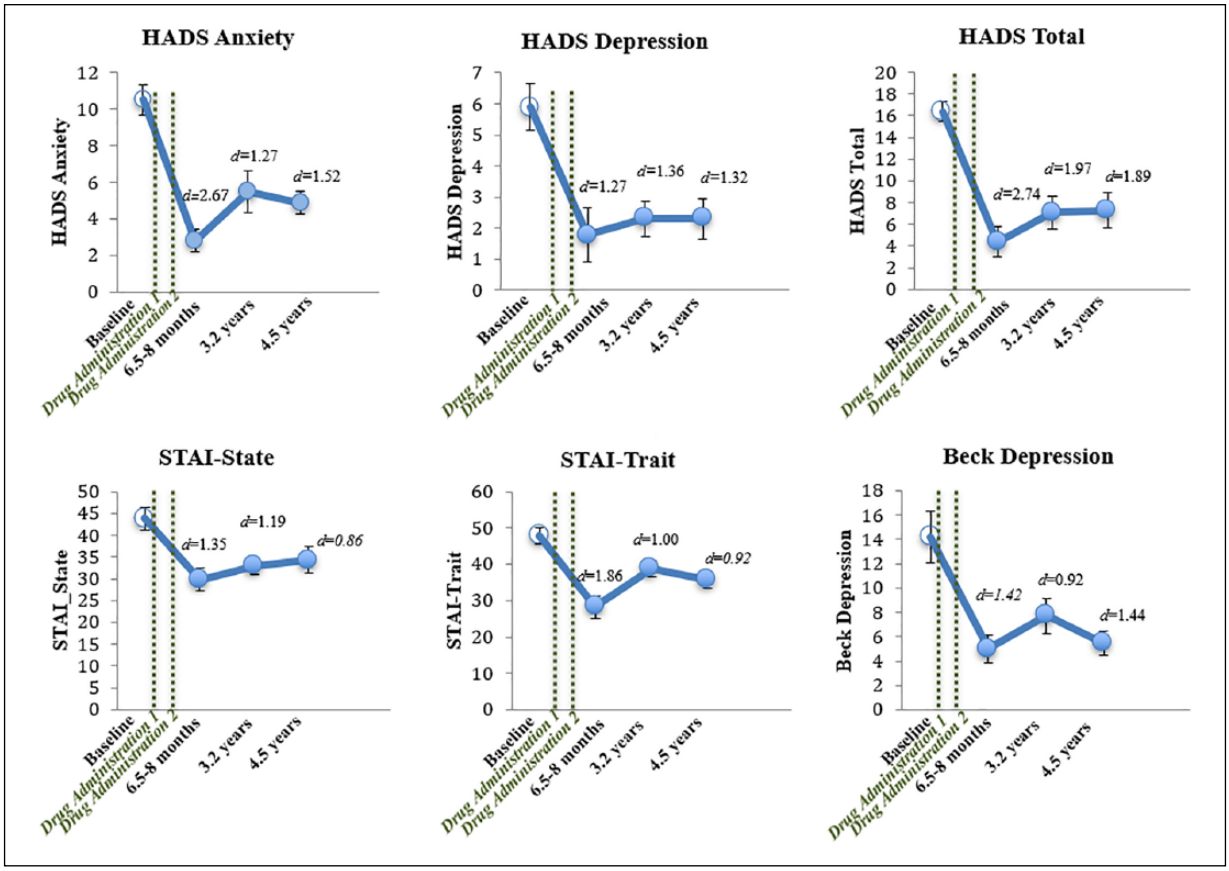

Figure 1. Primary outcome variables: cancer-related anxiety and depression (post-crossover).
Means (±standard error (SE)) for primary outcome measures for both dose-sequence groups combined are shown at the following time points: Baseline (N=16), 6.5 months (parent study endpoint; N=16), mean 3.2 years (first follow-up; N=15), and mean 4.5 years (second follow-up; N=14). Closed points represent significant within-subject differences relative to scores at baseline. Longitudinal within-subject effect sizes, represented as Cohen's d, are shown above time points. HADS: Hospital Anxiety and Depression Scale; STAI: State-Trait Anxiety Inventory.

significance, and increases in personal well-being. Ratings of these persisting effects were expressed as proportions.

Spearman rank correlation coefficients (for use in nonparametric tests) were calculated between total scores on the MEQ-30 assessed at the end of their psilocybin session days and change scores on primary and secondary measures between baseline and the second LTFU assessment.

To determine whether length of time between participants' psilocybin session and the LTFU predicted long-term clinical change, Spearman rank correlation coefficients were calculated between change scores on measures of anxiety, depression, and existential distress (i.e. second LTFU subtracted from two-weeks post-psilocybin) and the total number of days elapsed between each participant's unique individual psilocybin session and the date of their second LTFU assessment. Of note, the range of two-weeks post-psilocybin dose in comparison to the final long-term outcome was selected because the two-week post-dose assessment was the first LTFU point that included all primary and secondary measures.

Results

Primary outcomes

Results of MMRM analyses indicated sustained reductions at the first LTFU point since the final parent study (6.5-month) time point on all primary measures except the HADS-A and STAI-T. Analyses indicated statistically significant reductions relative to baseline on all of the primary measures measuring anxiety and depression at the 6.5-month, first and second LTFU points (see Figure 1 and Table 2). This represented large, statistically significant reductions in symptoms since baseline at the 6.5-month point (mean Cohen's d=1.90, range 1.27–2.67), first LTFU (mean Cohen's d=1.30, range 0.93–1.97), and second LTFU point (mean Cohen's d=1.41, range 0.86–1.89).

At the second LTFU point, 57% of participants showed a clinically significant anxiolytic response on the HADS-A. Seventy-one percent of participants reported clinically significant reductions in global psychological distress on the HADS-T, measuring anxiety and depression combined. Lastly, percentages of clinical responses for depression on the HADS-D and BDI ranged from 57–79%, and depression symptom remission rates ranged from 50–79% at the second LTFU (see Figure 2).

Secondary outcomes

There were significant reductions in hopelessness, demoralization and death anxiety at the 6.5-month, first and second LTFU points relative to baseline. These represented large, statistically significant reductions in symptoms since baseline at the 6.5-month point (mean Cohen's d=1.39, range 0.88–2.00), first LTFU (mean Cohen's

Table 2. Participant ratings on primary and secondary questionnaires.

Measure	Assessment time point			
	Baseline	6.5–8 months	3.2 years	4.5 years
HADS Anxiety	10.56 (0.93)	2.81 (0.95)[a]	5.50 (0.93)[a]	4.99 (0.98)[a]
HADS Depression	5.88 (0.71)	1.75 (0.73)[a]	2.25 (0.71)[a]	2.30 (0.75)[b]
HADS Total	16.45 (1.32)	4.38 (1.35)[a]	7.13 (1.32)[a]	7.34 (1.39)[a]
STAI State Anxiety	43.94 (2.51)	29.84 (2.58)[a]	33.00 (2.51)[b]	34.41 (2.67)[c]
STAI Trait Anxiety	47.81 (2.24)	28.23 (2.75)[a]	3.84 (2.85)[c]	35.78 (3.02)[b]
Beck Depression	14.19 (1.49)	5.09 (1.54)[a]	7.75 (1.49)[b]	5.45 (1.59)[a]
Demoralization	31.88 (2.61)	16.84 (2.67)[a]	13.29 (2.69)[a]	14.32 (2.76)[a]
Hopelessness	5.75 (0.51)	1.65 (0.52)[a]	2.29 (0.52)[a]	1.65 (0.54)[a]
Death anxiety	8.06 (0.78)	6.09 (0.79)[b]	5.68 (0.79)[b]	5.75 (0.81)[c]
Meaning/peace	19.43 (0.92)	26.34 (0.95)[a]	19.27 (0.95)	20.20 (0.98)
Faith	6.75 (1.32)	9.77 (1.34)[b]	9.31 (1.35)[c]	10.43 (1.37)[b]
Spiritual well-being	55.69 (3.16)	70.58 (3.12)[a]	59.85 (3.24)	65.04 (3.31)[c]
Social relationships	13.91 (0.75)	15.27 (0.76)	15.54 (0.77)	14.67 (0.79)
Environmental health	15.50 (0.53)	16.54 (0.53)[c]	16.72 (0.54)[c]	17.00 (0.55)[c]
Physical health	15.00 (0.69)	16.35 (0.70)[c]	16.33 (0.71)	13.89 (0.73)
Psychological health	13.58 (0.43)	15.70 (0.45)[a]	15.48 (0.45)[b]	14.80 (0.46)

HADS: Hospital Anxiety and Depression Scale; SD: standard deviation; STAI: State-Trait Anxiety Inventory.
Data are means (SDs) collapsed across both dose sequence groups (N=16, N=15, N=15, N=14 at baseline, 6.5 months, mean 3.2 years and mean 4.5 years, respectively). Supercripts indicate significant within-subject differences from baseline to time point ([a]$p<0.001$, [b]$p<0.01$, [c]$p<0.05$).

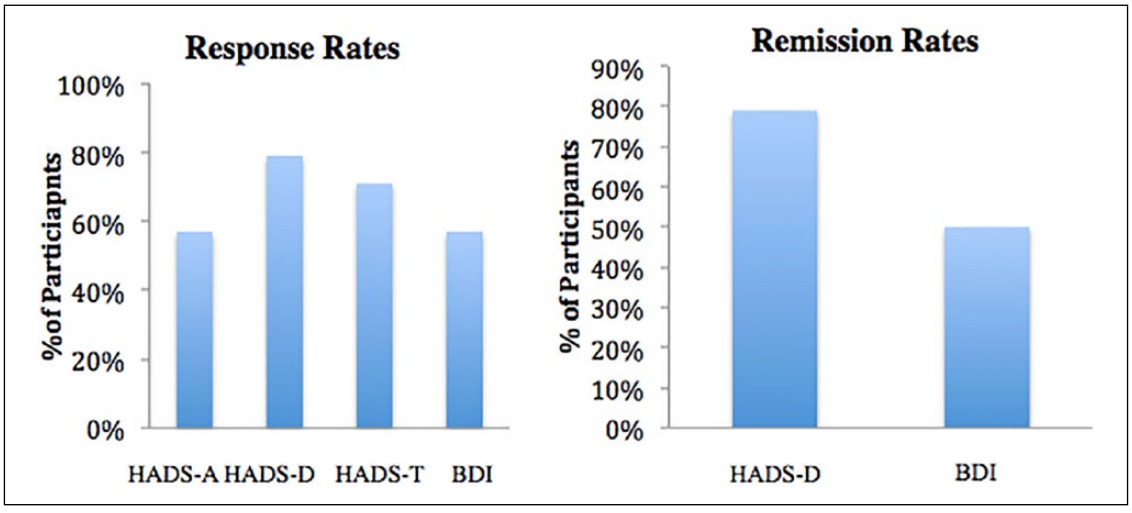

Figure 2. Percentage of participants with antidepressant or anxiolytic response rates and antidepressant symptom remission at final follow-up.
Data are percentages of participants (in both dose sequence groups combined) fulfilling criteria for antidepressant or anxiolytic response or antidepressant symptom remission (Hospital Anxiety and Depression Scale-Depression (HADS-D), Beck Depression Inventory (BDI)) at the 4.5-year point (second long-term follow-up; N=14). Clinical response was defined as 50% or greater decrease in each measure relative to baseline; symptom remission was defined as 50% or greater decrease in the measure relative to baseline and a score of ⩽7 on HADS-D or ⩽12 on BDI.

d=1.39, range 0.80–1.77), and second LTFU (mean Cohen's d=1.60, range 1.00–2.00). Results are presented in Figure 3. There were also significant improvements in spiritual well-being and faith domains (FACIT-Sp-12) at the second LTFU relative to baseline. Results on quality of life were mixed: there were increases on the psychological (i.e. self-esteem and emotional health) and environmental (i.e. financial resources, physical security, participation in recreational activities) dimensions of quality of life at the first LTFU, however, gains in psychological health at the first LTFU were not sustained at the second LTFU.

Mystical-type experience scores (MEQ-30) collected on participant's psilocybin dosing day in the parent study did not significantly correlate with primary outcome LTFU change scores (second long-term LTFU relative to the psilocybin dosing day) on any of the primary outcome measures of anxiety or depression.

Participant ratings of persisting effects are displayed in Figure 4. Participants indicated positive attributions to the psilocybin experience that persisted until the second LTFU. Seventy-one percent of participants continued to rate the psilocybin experience the single or top-five most personally meaningful experience(s) of their lives.

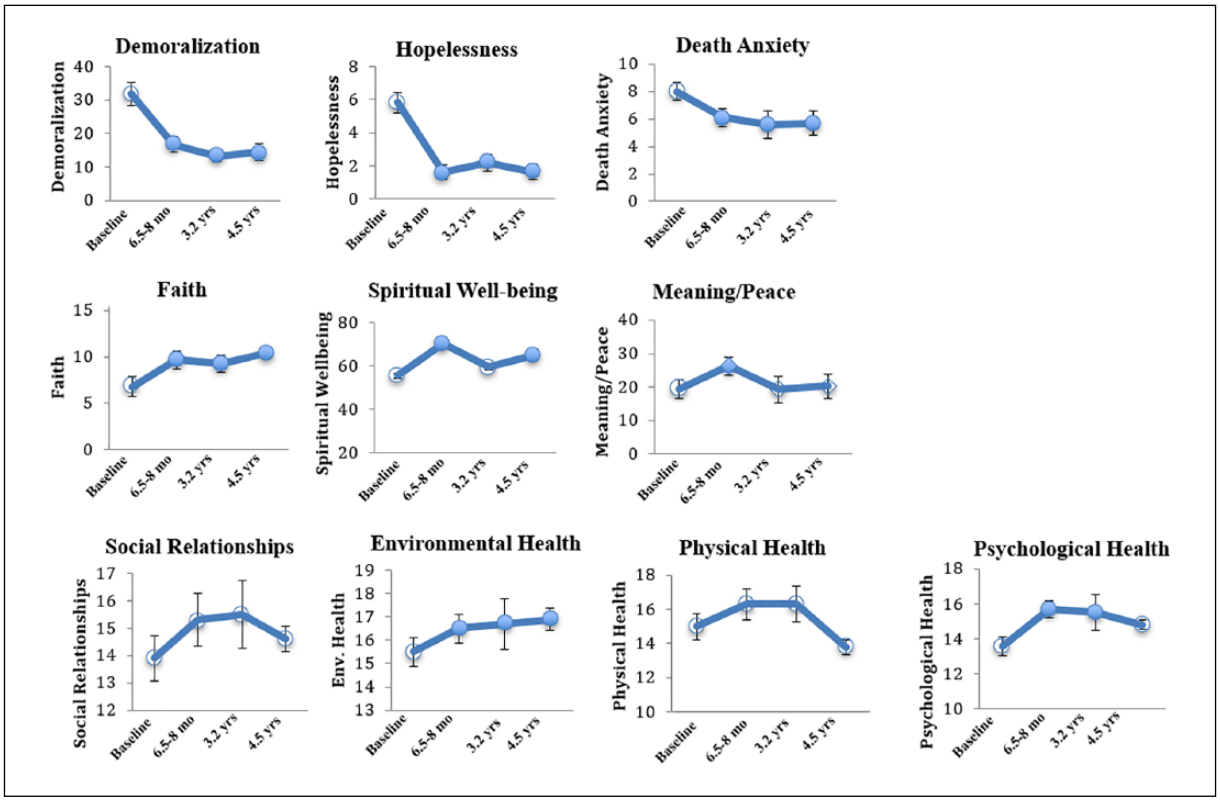

Figure 3. Secondary outcome measures: existential distress, spirituality, and quality of life.
Means (±standard error (SE)) for secondary outcome measures for participants (in both dose sequence groups combined) are shown at the following time points: Baseline (*N*=16), 6.5 months (parent study endpoint; *N*=16), mean 3.2 years (first follow-up; *N*=15), and mean 4.5 years (second follow-up; *N*=14). Closed points represent significant within-subject differences relative to scores at baseline.

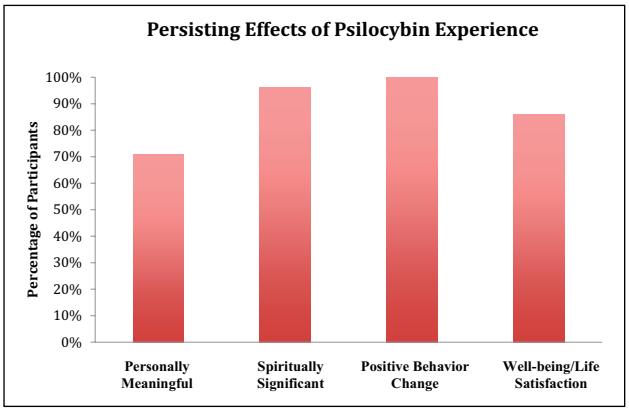

Figure 4. Persisting effects attributed to psilocybin administration.
Percentage of volunteers who endorsed persisting effects attributable to psilocybin administration on the Persisting Effects Questionnaire at the at the 4.5-year point (second long-term follow-up; *N*=14): percentage who endorsed "among the top five" or "the single most" personally meaningful experiences; "among the top five" or "the single most" spiritually significant experiences; "moderate," "strong" or "extreme" positive behavioral change; and "increased moderately" or "increased very much" well-being or life satisfaction.

Ninety-six percent rated the psilocybin experience the single or top-five most spiritually significant experience(s) of their lives. Participants appraised the psilocybin session as increasing life satisfaction or wellbeing at a rate of 86%. Lastly, 100% of volunteers reported "moderate," "strong" or "extreme" positive behavioral change attributed to the psilocybin experience. Cancer remission status (partial or complete remission versus an active diagnosis of cancer) did not significantly interact with any of the scores on primary or secondary outcome measures.

Length of time between psilocybin session and follow-up (i.e. second LTFU relative to each participant's two-week-post-psilocybin dosing date) correlated positively with depression and hopelessness change scores (second LTFU subtracted from two-weeks post-psilocybin dose scores) on the following measures: HAD-D (r=0.70, p<0.01) and HAI (r=0.69, p<0.01). Results are depicted in Figure 5.

Participants were asked open-ended questions about their psilocybin-assisted psychotherapy experience to further understand the enduring high ratings of persisting effects at the second LTFU. Table 3 presents verbatim written comments about the nature of their psilocybin-assisted psychotherapy experiences.

Discussion

This is the first report of long-term effects of psilocybin treatment in patients with cancer-related psychiatric and existential distress at two long-term follow-ups. The data suggest that psilocybin-assisted psychotherapy was associated with large and significant reductions in anxiety, depression, hopelessness, demoralization, and death anxiety, as well as improvements in spiritual well-being at an average of 3.2 and 4.5 years following psilocybin administration, after a

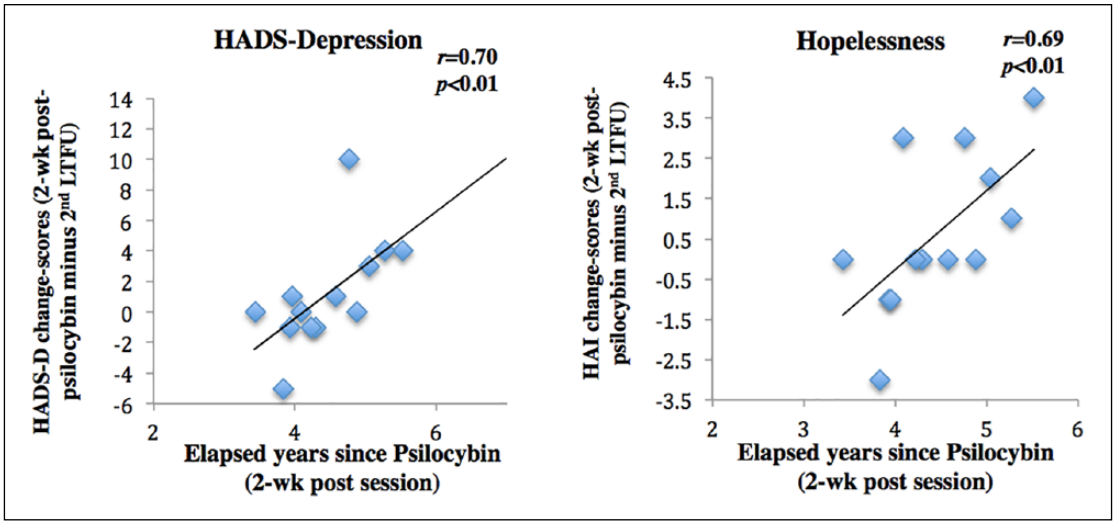

Figure 5. Relationship between time elapsed between psilocybin session and second long-term follow-up, and outcome measures assessed at two weeks after psilocybin session.

Each graph shows scores on an outcome measure assessed two weeks after participants' psilocybin session as a function of elapsed time between the two-week post-psilocybin date and each participant's second long-term follow-up date. Correlation coefficients and *p*-values are displayed. HADS: Hospital Anxiety and Depression Scale; LTFU: long-term follow-up.

Table 3. Verbatim written comments about the nature of the psilocybin experience from participants at the second long-term follow-up (LTFU). These comments were excerpted from a questionnaire that asked open-ended questions about positive changes attributed to the psilocybin-assisted therapy experience.

Volunteer	Verbatim comments
13	I'm more creative in my work and take more chances. I'm back to performing, like I did before. I bring more openness to my art. And connect to others on a more creative level.
14	It has given me a different perspective on my life and has helped me to move on with my life and not focus on the possibility of cancer recurring. I try not to hold onto or stress unimportant things.
15	[I experienced a] greater awareness of a spiritual connection to the universe. . . of the profound beauty of nature.
16	I've always been afraid of rejection. I experienced such overwhelming love in my psilocybin experience, that it gave me new confidence. I threw myself a birthday party and invited more people than I thought I ever could. They came! I think the extreme depth of love I felt changed the way I relate to others. [It] gave me a feeling that I have a right to be here and to enjoy life.
27	It's hard to explain. . . something in me softened, and I realized that everyone is just trying (mostly) to do the best they can. Even me. And that matters, since we are all connected.
28	[I] most certainly feel a stronger connection to a higher power due to the psilocybin experience, [as well as] greater openness towards others, more empathy, more interconnected with other people. I believe these changes are directly attributable to the psilocybin experience as well as the integration sessions afterwards.
34	There's a reckoning, which came with cancer, and this reckoning was enhanced by the psilocybin experience. I have a greater appreciation and sense of gratitude for being alive.
35	Once the thought that cancer is a part of your life becomes woven into the fabric of your being, you realize that this, or something similar, awaits many others who are unsuspecting. This compels you to relate to others from the perspective of compassion due to the changeable and temporary nature of our sense of who we are. Radical change is just around the corner regardless of how certain we are of our current state. We are children in our understanding of life until something reaches into your heart and announces itself. I understand the life process to be one of realization of our divine nature. This does not include any supernatural creature; it is a process of remembrance
36	[The] experience reinforced the understanding that we are all very much together, that [the] prevailing feeling in the end is love.
42	The psilocybin experience changed my thoughts about myself in the world. I see myself in a less limited way. I am more open to life. It has taken me out from under a big load of feelings and past issues in my life that I was carrying around.

crossover. The magnitudes of reductions relative to baseline in primary measures of anxiety and depression were large, with the largest effect sizes seen for global distress of combined anxiety and depression. Approximately 60–80% of participants continued to meet criteria for clinical antidepressant or anxiolytic response and remission at the second LTFU. At the second LTFU, participants overwhelmingly (71–100%) attributed subjective experiences of positive changes to the psilocybin-assisted psychotherapy

experience, reporting improved well-being or life satisfaction, and rating it among the most personally meaningful and spiritually significant experiences of their lives.

Due to the limitations of the crossover design of the parent study, it is not possible to attribute long-term improvements in psychiatric and existential distress directly to psilocybin-assisted psychotherapy. The majority of participants met criteria for an adjustment disorder (on the DSM-IV-TR) relative to cancer-related stressors at enrollment, and 71% reported entering partial or complete cancer remission at the second LTFU. Participants may have thus experienced naturalistic or spontaneous diminishment of distress and resolution of their adjustment disorders as they entered remission and approached the five-year cancer survival threshold. It is also possible that other psychiatric interventions received after the end of the parent trial accounted for improvements in depressive or anxious symptoms. However, this possibility is less likely given that in the follow-up assessment period only 8% of participants reported receiving any psychotherapy or pharmacotherapy specifically targeting cancer-related psychiatric distress.

These findings have meaningful implications for the clinical management of cancer-related existential distress. It is hopeful to consider the possibility that psilocybin-assisted psychotherapy could represent the first empirically-driven pharmacotherapy intervention to treat this indication. Existential distress is under-recognized and under-treated in cancer patients within Western medicine (Cepoiu et al., 2008; Gouveia et al., 2015). Among medical illnesses, depression and hopelessness associated with a diagnosis of cancer can serve as severe stressors and are well-known risk factors for suicidal ideation and completed suicides (Rosenfeld et al., 2011; Breitbart et al., 2000). The potential rapidity and long-term durability of psilocybin-assisted psychotherapy's effects represents a promising protective strategy against suicides. Future trials should carefully explore this application with cancer populations with chronic, passive suicidality, as there is preliminary evidence that psychedelic use may prevent suicidal ideation and behaviors (Hendricks et al., 2015; Johansen and Krebs, 2015).

An intriguing finding from our analyses was that the greater amount of time that had passed between participants' psilocybin session and the second LTFU predicted stronger reductions in subjective reports of depression and hopelessness during this period. The significance of this finding is unclear. However, it is interesting to consider that certain domains of cancer-related distress, particularly certain key domains of existential distress, could continue to improve rather than diminish over time in relation to a single psilocybin session. The extended follow-up is an important strength of this study as the vast majority of psycho-oncology RCTs to treat psychological distress report a follow-up period of typically no more than one year following treatment (Faller et al., 2013; Gasser et al., 2015; Stagl et al., 2015)

If it were established that psilocybin-assisted psychotherapy effectively treats cancer-related psychiatric and existential distress, it would be important to understand the neurobiological and psychological mechanisms of action. In our previous report, the psilocybin-facilitated mystical-type experience was found to partially mediate the effect of dose sequence on anxiolytic and antidepressant effects of psilocybin-assisted psychotherapy prior to the crossover, suggesting that acute aspects of participants' subjective experience may explain changes in psychiatric outcomes up to seven weeks (Ross et al., 2016). In the present study, a mystical-type experience was not associated with long-term changes at the LTFU points. A reduction in power might have weakened our ability to detect an effect as the sample size in this LTFU study was reduced by 50%. It is also possible that the mystical-type experience does not represent a significant psychological change mechanism accounting for psilocybin's therapeutic effects, or that other aspects of participants' experiences are more influential in determining longer-term response. However, given the growing body of evidence linking the intensity of the psilocybin-facilitated mystical-type experience to therapeutic improvements across a range of psychiatric and addictive disorders (Bogenschutz et al., 2015; Garcia-Romeu et al., 2014; Griffiths et al., 2016; Pahnke et al., 1969; Roseman et al., 2019; Ross et al., 2016), it is important to further explore this potential psychological mechanism of action in additional adequately-powered RCTs. It would also be important to explore other potential psychological change mechanisms of psilocybin-assisted psychotherapy in this patient population.

One such mechanism may relate to rapid and enduring shifts in cognition. Classic psychedelics offer a rapid means of dismantling habitual mental templates that, over time, may rigidify one's attention and behavior—patterns that are associated with various psychiatric pathologies (Carhart-Harris, 2018; Carhart-Harris and Friston, 2019). Psychedelic-induced states of consciousness are, instead, associated with increases in trait openness and cognitive flexibility (Carhart-Harris et al., 2012; Kuypers et al., 2016). In an open-label trial of psilocybin in patients with treatment-resistant depression participants reported increased trait openness, with significant increases in the following sub-traits: "openness to values" (i.e. valuing open-mindedness and psychological flexibility) and "openness to actions" (i.e. readiness to try and engage in new activities; Erritzoe et al., 2018). Being open to novel and more constructive ways of thinking, feeling and behaving is one of the central goals of contemporary evidence-based psychotherapies (e.g. cognitive behavioral therapy and Acceptance Commitment Therapy (Hayes et al., 2012)), and enhanced cognitive and psychological flexibility may constitute a psychological mechanism mediating psilocybin-assisted psychotherapy's antidepressant and anxiolytic effects (Watts and Luoma, 2020). Further, given the link between enhanced mystical-type states and enduring increases in trait openness (MacLean et al., 2011), it is possible that certain features of the mystical-type state (e.g. dissolution of boundaries and feelings of unity) lead one to develop enduring increases in psychological flexibility when coupled with supportive psychotherapy. The psilocybin experience may have enabled participants to establish a new inner framework from which they could flexibly avail themselves of resources internally and in their environment to cope with life stressors, particularly stressors associated with their cancer diagnoses.

It is also possible that other aspects of the acute psilocybin experience, such as challenging (Barrett et al., 2016) or emotional breakthrough experiences (Roseman et al., 2019), are more influential in explaining long-term changes of psilocybin-assisted psychotherapy. The resolution and integration of difficult emotions may be particularly relevant for clinical populations such as cancer patients, and such emotional processing may support the development of greater psychological flexibility and emotional regulation in the long-term (Lane et al., 2015). It would be important to assess these potential psychological change mechanisms

in future trials that are adequately designed and powered. These theories are supported by a growing consensus that serotonin 2A signaling mediates functional shifts in connectivity in cortico-striato-thalmo-cortical pathways (Preller et al., 2019), increased entropy in the brain (Carhart-Harris, 2018), and disruption of activity within the default mode network, a brain system that is associated with self-referential information processing and mind-wandering (Carhart-Harris and Nutt, 2017; Carhart-Harris and Goodwin, 2017; Ly et al., 2018). These theories are also consistent with the quantitative (Ross et al., 2016) and qualitative (Belser et al., 2017; Swift et al., 2017) findings from the parent trial and the present study of highly memorable, meaningful, and spiritually significant effects attributed to the psilocybin experience. We strongly believe, however, that an isolated experience with psilocybin does not inherently confer therapeutic benefits. Rather, the development of an enduring therapeutic experience is contingent on contextual factors, such as the presence of skilled therapists or guides, which facilitate a larger psychotherapeutic process. It is, therefore, important to recognize that purely neurobiological interpretations regarding brain activity during acute phases of a psilocybin experience will not adequately capture the dynamics of a psychotherapeutic process that may unfold in the weeks or months thereafter, fostering enhanced meaning and greater well-being.

Limitations

There were several limitations of this study, which suggest directions for future research. The use of a crossover design in the parent study at seven weeks permitted an assessment of acute and enduring effects among both dosesequence groups combined but does not enable a true control group for comparison after seven weeks. It is also not possible to separate the effects of the psilocybin medication from those of the psychotherapeutic session and context into which the medication session was embedded. Additionally, the small number of participants participating in this follow-up reduces statistical power, which could increase the effect of outliers on outcomes, and affects generalizability of the findings. Further, the sample was not ethnically, racially or socioeconomically representative of cancer patients in the USA (e.g. 94% of the sample was non-Hispanic Caucasian, and 86% were well-educated and from higher socioeconomic backgrounds), which substantially limits the generalizability of our findings to other cultural groups. Across modern trials of psychedelic-assisted therapies, minority groups are greatly underrepresented, and future investigators should make concerted efforts to address this issue by developing research-community collaborations to decrease prohibitive barriers to participation (George et al., 2019; Michaels et al., 2018). Future studies should also endeavor to include a larger sample of participants with a placebo-control group, without a crossover, to establish a more rigorous experimental design.

Conclusion

In summary, the findings of this LTFU study represent the first suggestion of persistent long-term effects of psilocybin-assisted psychotherapy for cancer-related distress. Although limited conclusions can be drawn regarding efficacy due to the crossover design, results suggests that the treatment continues to be associated with reductions in anxiety, depression, hopelessness, demoralization, and death anxiety up to an average of 4.5 years following a single psilocybin session in conjunction with psychotherapy. Theories regarding neurobiological and psychological change mechanisms remain speculative and exploratory. Further research will need to validate the main findings of the parent trial and this LTFU article with a fully experimental design in order to empirically establish the use of psilocybin-assisted psychotherapy to treat the psychiatric and existential distress of those with life-threatening cancer diagnoses.

An advanced experimental design of psilocybin-assisted psychotherapy would likely include a larger sample size (i.e. N=200) that is nationally representative of cancer patients. It would also include randomized, parallel groups without a crossover, use of an adequate placebo control group, measures taken to minimize blinding and expectancy effects, and the use of valid and reliable outcome measures. It might also include design elements that would allow for exploration of potential neurobiological (e.g. growth factor expression, functional connectivity, neuroplasticity) and psychological (e.g. mystical experience, personality, psychological flexibility, emotional breakthroughs and insights, challenging experiences) mechanisms of action of psilocybin-assisted therapy.

Funding for psychedelic research in the USA remains mostly limited to the private sector at present time. It would be an historic and important milestone if the National Institutes of Health were to fund advanced research exploring the therapeutic potential of psilocybin-assisted psychotherapy in patients with life-threatening cancer and concomitant psychiatric and existential distress. If the Food and Drug Administration were to sanction this next phase of research (i.e. phase III trials) for this clinical indication, and favorable findings were to emerge, it could help to form a pathway for psilocybin to become re-scheduled and clinically available for cancer patients. It would represent a major paradigm shift in the psycho-oncological approach and care of patients with cancer. The use of psilocybin-assisted psychotherapy for those with life-threatening cancer could be especially useful in helping patients approach their lives with enhanced psychological, emotional, and spiritual wellbeing.

Declaration of conflicting interests

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JAMA Psychiatry | Original Investigation

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

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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* = 2.2; 95% CI, 1.4-3.0; *P* < .001) and week 8 (Cohen *d* = 2.6; 95% CI, 1.7-3.6; *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* = 3.0; 95% CI, 1.9-4.0; *P* < .001), which remained statistically significantly reduced through the week 4 follow-up (6.0 [5.7]; Cohen *d* = 3.1; 95% CI, 1.9-4.2; *P* < .001). In the overall sample, 16 participants (67%) 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]

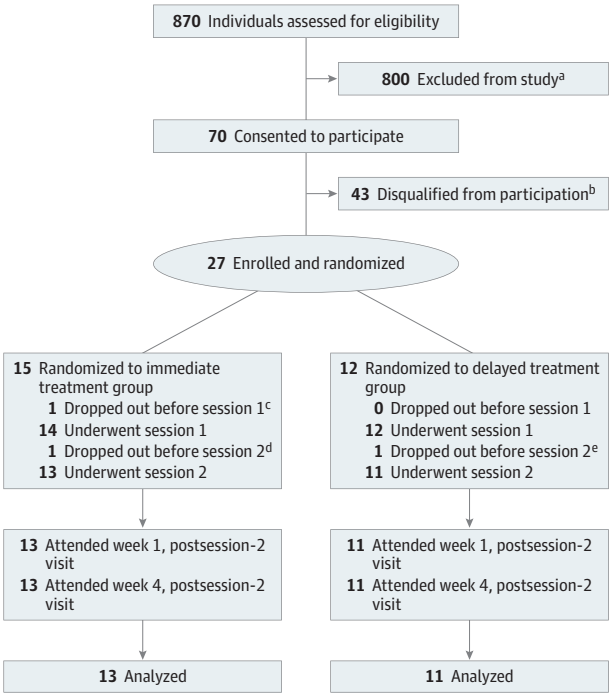
Participants received no monetary compensation for undergoing the intervention. However, participants received a total of $200 for completing 2 magnetic resonance imaging sessions.

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.

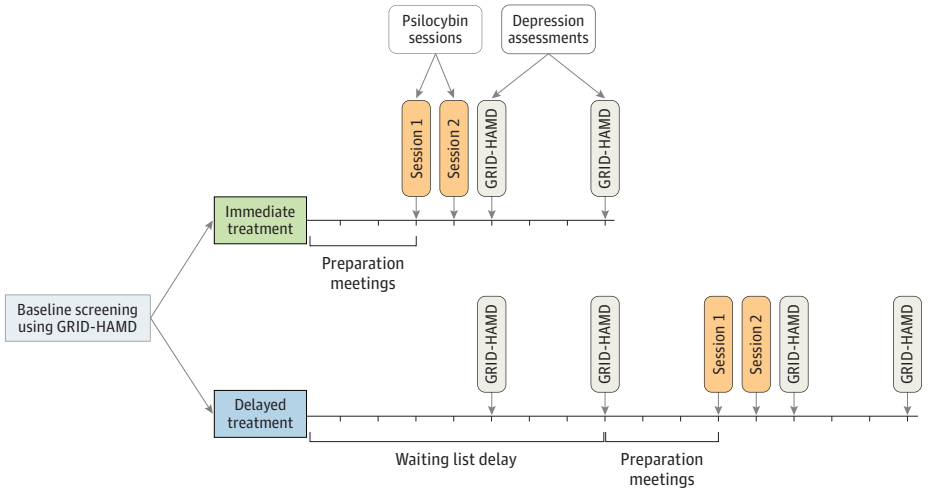
[b] People were deemed ineligible during in-person screening if they had a psychiatric condition judged to be incompatible with establishment of rapport or safe exposure to psilocybin (n = 17); did not have confirmed *DSM-5* diagnosis of MDD (n = 7); had a recent history of moderate to severe substance 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

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*.

study of psilocybin[16] found a large effect of a high psilocybin dose (compared 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).

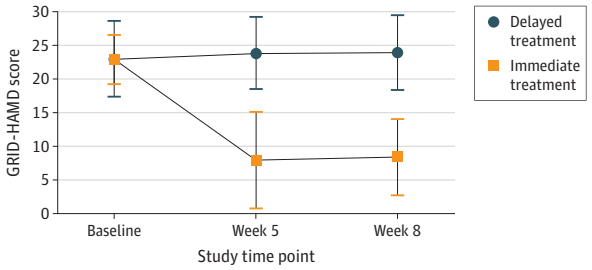
Follow-up planned comparisons included independent samples *t* tests to compare week 1 with week 4 GRID-HAMD scores in the immediate treatment condition group (corresponding to the week 5 and week 8 time points in the delayed treatment condition group). Within-participant (n = 24) treatment effect was 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

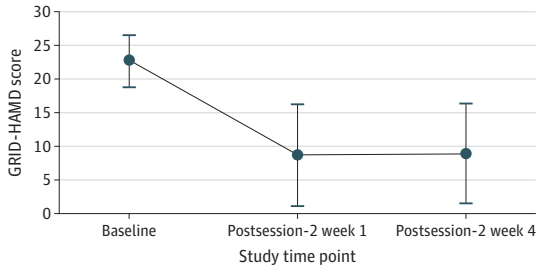
A total of 27 participants were randomized, of whom 24 (89%) completed the intervention as well as the postsession assessments at weeks 1 and 4; specifically, 13 were randomized to the immediate treatment group and 11 to the delayed treatment group (Figure 1). The **Table** shows the demographic characteristics 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).

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* = 2.2; 95% CI, 1.4-3.0; *P* < .001) and week 8 (Cohen *d* = 2.6; 95% CI, 1.7-3.6; *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* = 3.6; 95% CI, 2.2-5.0; *P* < .001) and week 4 postsession-2 follow-up (Cohen *d* = 3.6; 95% CI, 2.2-4.9; *P* < .001).

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

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* = 2.2; 95% CI, 1.4-3.0; *P* < .001) and at week 8 (Cohen *d* = 2.6; 95% CI, 1.7-3.6; *P* < .001) (eTables 1-3 and eResults in Supplement 2).

After the psilocybin session, 16 participants (67%) 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* = 3.6; 95% CI, 2.2-5.0; *P* < .001) and week 4 (Cohen *d* = 3.6; 95% CI, 2.2-4.9; *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* = 3.0; 95% CI, 1.9-4.0; *P* < .001). This substantial decrease remained through week 4 after session 2 (6.0 [5.7]; Cohen *d* = 3.1; 95% CI, 1.9-4.2; *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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Concept and design: Davis, Barrett, May, Cosimano, Johnson, Griffiths.
Acquisition, analysis, or interpretation of data: Davis, Barrett, May, Sepeda, Johnson, Finan, Griffiths.
Drafting of the manuscript: Davis, Barrett, May, Cosimano, Sepeda, Griffiths.
Critical revision of the manuscript for important intellectual content: Davis, Barrett, May, Sepeda, Johnson, Finan, Griffiths.
Statistical analysis: Davis, Griffiths.
Obtained funding: Barrett, Griffiths.
Administrative, technical, or material support: Davis, Barrett, May, Cosimano, Sepeda, Finan, Griffiths.

Supervision: Davis, Barrett, May, Cosimano, Johnson, Griffiths.

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Data Sharing Statement: See Supplement 3.

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ORIGINAL INVESTIGATION

Psilocybin with psychological support for treatment-resistant depression: six-month follow-up

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Abstract
Rationale Recent clinical trials are reporting marked improvements in mental health outcomes with psychedelic drug-assisted psychotherapy.
Objectives Here, we report on safety and efficacy outcomes for up to 6 months in an open-label trial of psilocybin for treatment-resistant depression.
Methods Twenty patients (six females) with (mostly) severe, unipolar, treatment-resistant major depression received two oral doses of psilocybin (10 and 25 mg, 7 days apart) in a supportive setting. Depressive symptoms were assessed from 1 week to 6 months post-treatment, with the self-rated QIDS-SR16 as the primary outcome measure.
Results Treatment was generally well tolerated. Relative to baseline, marked reductions in depressive symptoms were observed for the first 5 weeks post-treatment (Cohen's $d = 2.2$ at week 1 and 2.3 at week 5, both $p < 0.001$); nine and four patients met the criteria for response and remission at week 5. Results remained positive at 3 and 6 months (Cohen's $d = 1.5$ and 1.4, respectively, both $p < 0.001$). No patients sought conventional antidepressant treatment within 5 weeks of psilocybin. Reductions in depressive symptoms at 5 weeks were predicted by the quality of the acute psychedelic experience.
Conclusions Although limited conclusions can be drawn about treatment efficacy from open-label trials, tolerability was good, effect sizes large and symptom improvements appeared rapidly after just two psilocybin treatment sessions and remained significant 6 months post-treatment in a treatment-resistant cohort. Psilocybin represents a promising paradigm for unresponsive depression that warrants further research in double-blind randomised control trials.

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Introduction

Psilocybin is a naturally occurring plant alkaloid that is being increasingly researched as treatment for a range of different psychiatric disorders (Carhart-Harris and Goodwin 2017). Four separate trials have reported improvements in depressive symptoms after psilocybin-assisted psychotherapy (Griffiths et al. 2016; Ross et al. 2016; Grob et al. 2011; Carhart-Harris et al. 2016), including one in which 'treatment-resistant depression' was the primary criterion for inclusion (Carhart-Harris et al. 2016). Psilocybin has shown promise in the treatment of obsessive compulsive disorder (Moreno et al. 2006), alcohol (Bogenschutz et al. 2015) and tobacco addiction (Johnson et al. 2014) and anxiety related to terminal diagnoses (Griffiths et al. 2016; Ross et al. 2016; Grob et al. 2011). Treatment procedures typically involve psychological preparation prior to one or two therapist-supported drug sessions followed by psychological integration. Using a consistent model (i.e. involving appropriate psychological support), sustained improvements in well-being in healthy individuals were observed after a single dose of psilocybin in a double-blind design incorporating an active placebo (Griffiths et al. 2008).

Studies involving other serotonergic psychedelics combined with psychological support have found similarly promising outcomes: Sustained reductions in end-of-life anxiety were observed after LSD-assisted psychotherapy (Gasser et al. 2014), and reduced depressive symptoms were seen after ayahuasca in patients with 'recurrent depression' (Osorio Fde et al. 2015; Sanches et al. 2016). Naturalistic, observational studies of ayahuasca support its long-term well-being promoting and anti-addiction properties (Thomas et al. 2013; Bouso et al. 2012) and a recent population survey found lower rates of suicidality and psychological distress in association with psychedelic drug use (Hendricks et al. 2015)—an anomalous association for a drug of potential misuse. Drug experts and users have consistently rated psilocybin as the least harmful and potentially 'most beneficial' drug of potential misuse (Carhart-Harris and Nutt 2013; van Amsterdam et al. 2015)—although the influence of *context* (e.g. expectations and environmental factors) on potential harms and benefits has been much emphasised (Hartogsohn 2016; Carhart-Harris et al., in review). Further evidence favouring the therapeutic potential of psychedelics can be found in literature documenting the extensive research carried out with these compounds in the mid-twentieth century, e.g. two relevant meta-analyses have found positive safety and efficacy data for LSD for alcohol dependence (Krebs and Johansen 2012) and mood disorders (Rucker et al. 2016). See Carhart-Harris and Goodwin (2017) for a review of historical and recent trials with psychedelics.

Like all serotonergic psychedelics, psilocybin initiates its characteristic effects via serotonin 2A receptor (5-HT2AR) agonism (Vollenweider et al. 1998). 5-HT2AR signalling has been associated with better responses to conventional antidepressants (Qesseveur et al. 2016; Petit et al. 2014), and preclinical work indicates that 5-HT2AR signalling may mediate (at least some of) the therapeutic effects of SSRIs (Nic Dhonnchadha et al. 2005; Buchborn et al. 2014). Paradoxically, 5-HT2AR antagonists have been found to augment the antidepressant effects of SSRIs (Ostroff and Nelson 1999) and many effective antidepressant augmentation medications have 5-HT2AR antagonist properties (Carpenter et al. 1999). This paradox implies that 5-HT2AR agonism *and* antagonism can achieve consistent ends, in terms of alleviating depressive symptoms, but via different mechanisms (see Carhart-Harris et al. (2017) and Carhart-Harris and Nutt (2017) for a relevant discussion).

The present report documents an extension to our recently published pilot study assessing psilocybin with psychological support for treatment-resistant depression. The number of patients treated was increased from 12 to 20 and the follow-up period extended from 3 to 6 months.

Methods

Approvals and drug source

This clinical trial received a favourable opinion from the National Research Ethics Service (NRES) London-West London, was sponsored and approved by Imperial College London's Joint Research and Complication Organisation (JRCO), was adopted by the National Institute of Health Research (NIHR) Clinical Research Network (CRN) and was reviewed and approved by the Medicines and Healthcare products Regulatory Agency (MHRA). A Home Office Licence for storage and dispensing of Schedule One drugs was obtained. Psilocybin was obtained from THC Pharm (Frankfurt) and formulated into the investigational medicinal product (5 mg psilocybin in size 0 capsules) by Guy's and St Thomas' Hospital's Pharmacy Manufacturing Unit (London, UK).

Study design

This was an open-label feasibility study in 20 patients with treatment-resistant depression. Treatment involved two oral doses of psilocybin (10 and 25 mg), 7 days apart. The primary outcome was mean change in the severity of self-reported (SR) depressive symptoms (measured primarily with the 16-

item Quick Inventory of Depressive Symptoms, QIDS-SR16) from baseline to specific time points after the high-dose psilocybin session (henceforth referred to as 'post-treatment'). QIDS-SR16 ratings were collected 1–3 and 5 weeks and 3 and 6 months post-treatment, with 5 weeks post-treatment regarded as the primary endpoint. BDI (depression) and STAI (anxiety) ratings were collected at 1 week and 3 and 6 months. SHAPS (anhedonia) was collected at 1 week and 3 months and HAM-D (depression, clinician-administered) and GAF (global functioning, clinician administered) ratings were collected at 1 week only. These secondary measures were collected to enable comparisons to be made with other studies that use the same measures. For this reason and since they were highly correlated with the primary outcome measure, we chose not to correct for their use. A revised α of 0.05/6 = 0.0083 for the six post-treatment QIDS-SR16 contrasts vs baseline was used however.

Trial procedures

Full details of trial procedures can be found in Carhart-Harris et al. (2016). Briefly, patients contacted the study team after which a telephone screen was organised with the main study psychiatrist. After checking eligibility criteria, candidates were invited for a screening visit at the Imperial Clinical Research Facility (ICRF) at the Hammersmith Hospital. This comprised of informed consent, documenting mental and physical health backgrounds, a psychiatric interview (MINI-5) to confirm diagnosis, physical examination, routine blood tests, ECG, urine test for drugs of abuse and pregnancy where relevant, a breathalyser and the completion of baseline assessments.

The main inclusion criteria were as follows: unipolar major depression of at least moderate severity (16+ on the 21-item HAM-D) and no improvement despite two courses of pharmacologically distinct antidepressant medications for an adequate duration (6 weeks minimum) within the current episode. Main exclusion criteria were as follows: a current or previously diagnosed psychotic disorder or an immediate family member with a diagnosed psychotic disorder.

Patients' mental health histories were confirmed with their GP or psychiatrist prior to study entry. With the exception of patient 2 (Table 1), eligible patients medicated with an antidepressant were advised to stop this for the trial, to avoid suspected attenuation of psilocybin's effects (Bonson et al. 1996). This was done in a tapered manner under careful supervision from the study psychiatrist. Washout occurred over at least 2 weeks prior to study entry, with the exception of patient 6, who stopped tramadol use only after the first psilocybin session (when the tramadol use was discovered).

Eligible patients attended a pretreatment MRI scan and psychological preparation visit, followed by two dosing sessions, separated by 1 week. In the first session, patients received 10 mg psilocybin and in the second, 25 mg. Patients were seen the following day for debriefing and a post-treatment MRI scan, and for one final time 1 week after the 25-mg session. Subsequent follow-up measures were collected remotely. Patients emailed their completed questionnaires to the study team. Six-month follow-up interviews were carried out by RW with all 20 patients and the relevant qualitative data are reported elsewhere (Watts et al. 2017).

Reporting Side effects

Side effects were documented based on patient reports in response to the question: "Have you experienced any side effects in relation to the treatment?" This was asked at all post-treatment visits and any spontaneously reported or observed side effects were also documented.

Psychological support

Psychological support comprised of three components: (1) preparation (P), (2) acute and peri-acute support (S) and (3) integration (I). (1) Preparation (P) involves getting to know the patient and his/her background, building a relationship of trust and providing some information on what can be expected from psilocybin and how best to navigate its effects. (2) Support (S) involves being physically and emotionally present for the patient before, during and after the acute drug session. It may incorporate empathetic listening and reassurance, for example. (3) Integration (I) involves non-judgmental listening to the patient's testimony after his/her experience and may occasionally feature some interpretation regarding the content of the experience and its potential meaning, as well as advice regarding maintaining and cultivating positive changes in outlook and lifestyle. We assign the acronym PSI to these core components of psychological support.

11-Dimension altered states of consciousness (11D-ASC) questionnaire

This is a 94-item questionnaire, of which 44 items are scored. The 44 items are factorised according to a previous validation paper (Studerus et al. 2010). Each item is scored as in a visual analogue scale with the upper anchor reading "much more than usual" and the bottom one reading "no more than usual". Patients performed the 11D-ASC at the end of each dosing day when the subjective effects of psilocybin had subsided to a negligible level; however, ratings were done with reference to the period when effects were most intense. *t* tests with Bonferroni correction (revised α = 0.05/11 = 0.0045) contrasted scores for the 10- and 25-mg dose sessions.

Table 1 Baseline characteristics and demographics: SSRI = selective serotonin reuptake inhibitor, SNRI = serotonin-noradrenaline reuptake inhibitor, NDRI = noradrenaline-dopamine reuptake inhibitor, NSSRI = noradrenaline and specific serotonin reuptake inhibitor, MAOI = monoamine oxidase inhibitor, Na + channel blocker = sodium channel blocker (e.g. lithium), TCA = tricyclic antidepressant, SARI = serotonin antagonist and reuptake inhibitor (e.g. trazodone), DRI = dopamine reuptake inhibitor. CBT = cognitive behavioural therapy, MBT = mindfulness CBT, CNT = cognitive narrative therapy, GT = group therapy, CS = counselling, JA = Jungian analysis

Number	Sex	Age (years)	Ethnicity	Employment status	Illness duration (years)	QIDS-16	BDI	HAM-D	STAI	Past meds	Past psychotherapy	Education	Weekly alcohol	Previous psilocybin
1	Female	43	Black	Employed	30	19	36	19	72	SSRI (two), SNRI (two), NDRI, NSSRI, MAOI	None	Masters	1	0
2	Male	40	Hispanic	Unemployed	25	20	33	28	76	SSRI (two), SNRI, NDRI, NSSRI, Na + channel blocker (two), ketamine, TCA	CNT	Masters	0	0
3	Male	37	White	Employed	17	22	22	18	63	SSRI (two), SNRI	CBT, GT	College post A-levels	0	0
4	Female	30	White	Studying	10	14	26	18	67	NDRI, NSSRI	CBT	Postgrad	0	1
5	Male	34	White	Unemployed	12	19	38	25	71	SSRI (three), TCA	CBT, MBT	Degree	0	0
6	Female	57	White	Unemployed	29	19	39	23	78	SSRI (four), SNRI, SARI	CS	Degree	2	2
7	Male	52	White	Unemployed	27	18	33	22	57	TCA, SARI	CS, MBT	GCSE	0	3
8	Female	37	White	Employed	17	19	39	17	71	SSRI (two), TCA	CS	Degree	2	0
9	Male	37	White	Unemployed	15	20	32	26	71	SSRI (three), SNRI	CS, CBT	Masters	6	0
10	Female	36	Black	Unemployed	8	21	47	28	75	SSRI (two), NSSRI	CS	Left uni	18	3
11	Female	64	White	Employed	15	18	24	16	72	SSRI (four), SNRI (two), NDRI, MAOI, Na + channel blocker, SARI, DRI	CBT	PhD	1	3
12	Male	45	White	Employed	8	21	35	17	68	SSRI, TCA	CBT	Uni	0	0
13	Male	27	White	Employed	7	18	29	26	55	SSRI, TCA, SARI, NDRI	CBT	Masters	8	0
14	Male	49	White	Unemployed	30	23	36	29	70	SSRI (four), SNRI, TCA, NDRI	JA, GT	Degree	0	1
15	Male	56	Black	Unemployed	30	25	44	36	66	SSRI, SARI	CBT	Degree	0	0
16	Male	42	White	Unemployed	22	17	45	29	69	SSRI (three), SARI (two), TCA	None	Degree	0	0
17	Male	31	Asian	Unemployed	6	19	44	20	66	SSRI, SNRI	None	Left school	0	1
18	Male	58	White	Part retired	10	16	28	28	61	SSRI (two), SARI	JA	Degree	0	0
19	Male	62	White	Retired	15	17	42	24	74	SSRI (two), TCA, pregabalin	JA	Masters	15	0
20	Male	44	White	Unemployed	20	14	27	28	68	SSRI (three), SARI, SNRI, Na + channel blocker, TCA, MAOI	CBT, MBT	Degree	20	0
Group	6 females	44.1 (11)	15 White	11 Unemployed	17.7 (8.5)	19 (2.-7)	35 (-7-.-4)	23.9 (5.-4)	68.5 (6.-0)	4.6 (2.6)	17 psychotherapy	18 higher ed	3.7 (6.5)	0.7 (1.1)

Data analysis

Two-tailed paired *t* tests were performed for all pre- vs post-treatment QIDS-S16 contrasts, with Bonferroni corrected α of 0.05/6 = 0.0083 for the six post-treatment time intervals. 95% confidence intervals (CI) are provided. Effect sizes were calculated using Cohen's *d* values for dependent data. We chose not to correct for additional clinical measures beyond correcting for QIDS-SR16 changes at multiple time points. This decision was made so as to avoid introducing type 2 errors through overly conservative correction and because of the high covariance between clinical measures (see "Results" section). For transparency, we provide all relevant *p* values and effect sizes.

Results

Patients

One hundred and twenty people expressed an interest in the study. Seventy-four were considered appropriate for a telephone screen, from which 29 were invited for a screening visit. Twenty were ultimately recruited for the trial and 19 completed all measures. Data on 12 of the 20 have been previously reported (Carhart-Harris et al. 2016) and these 12 are included in the present analysis. Patients' demographic and clinical characteristics are shown in Table 1. Eighteen of the 20 patients met the criteria for severe or very severe depression at baseline (QIDS-SR16 score of ≥ 16); the remaining two meeting the criteria for "moderate" depression (QIDS-SR16 score ≥ 11, < 16). The median number of (lifetime) failed previous medications was 4, the mean was 4.6 ± 2.6 and the maximum was 11. The mean duration of illness of the sample was 17.7 ± 8.4 years (range = 7–30 years), as assessed by the question: "For how long has your current depression lasted?" Note that none of the demographic variables were predictive of treatment response, including past use of psilocybin.

Data were analysed for the 19 who completed all assessment time points. Relative to baseline, QIDS-SR16 scores were significantly reduced at all six post-treatment time points ($p < 0.001$), with the maximum effect size at 5 weeks (− 9.2, 95% CI = − 11.8 to − 6.6, $t = -7.2$, $p < 0.001$, Cohen's $d = 2.3$) (see Fig. 1). Of the 19 patients who completed all assessments, all showed some reduction in depression severity at 1 week and these were sustained in the majority for 3–5 weeks. Changes in HAM-D ratings from baseline to 1-week post-treatment showed a reasonable correspondence with changes in QIDS-SR16 data across the same period ($r = 0.61$, $p < 0.001$) and the relationship between the QIDS-SR16 and BDI at 1 week was very strong ($r = 0.81$, $p < 0.001$).

BDI scores were significantly reduced at 1 week (mean reduction = − 22.7, 95% CI = − 17.6 to − 27.8, $p < 0.001$), 3 months (mean reduction = − 15.3, 95% CI = − 8.7 to − 21.9, $p < 0.001$) and 6 months post-treatment (mean reduction = − 14.9, 95% CI = − 8.7 to − 21.1, $p < 0.001$); STAI-T anxiety scores were significantly reduced at 1 week (mean reduction = − 23.8, 95% CI = − 16.5 to − 31.1, $p < 0.001$), 3 months (mean reduction = − 12.2, 95% CI = − 6.1 to − 18.3, $p < 0.001$) and 6 months post-treatment (mean reduction = − 14.8, 95% CI = − 8.1 to − 21.6, $p < 0.001$); SHAPS anhedonia scores were significantly reduced at 1 week (mean reduction = − 4.6, 95% CI = − 2.6 to − 6.6, $p < 0.001$) and 3 months post-treatment (mean reduction = − 3.3, 95% CI = − 1.1 to − 5.5, $p = 0.005$); HAM-D scores were significantly reduced at 1 week post-treatment (mean reduction = − 14.8, 95% CI = − 11 to − 18.6, $p < 0.001$); and GAF scores were significantly increased 1 week post-treatment (mean increase = + 25.3, 95% CI = 17.1 to 33.5, $p < 0.001$)—see Table 2.

Treatment was generally well tolerated and there were no serious adverse events. One patient became uncommunicative during the peak of his 25-mg psilocybin experience but this normalised after the acute drug effects had abated. Follow-up discussions revealed that his experience had been "blissful" and beneficial but also overwhelming (see supplementary file). Regretfully, this patient chose not to complete further follow-up measures, with the exception of the QIDS-SR16 and BDI scores at 6 months post-treatment. Follow-up scores were 25 (QIDS) and 40 (BDI) at 6 months. See Watts et al. (2017) for more details about individual cases.

A brief note: this experience, combined with evidence supporting the importance of patient-therapist rapport in the psychedelic treatment model (e.g. Carhart-Harris et al., in review), has motivated us to revise the exclusion criteria for future psilocybin trials, i.e. with "psychiatric condition judged to be incompatible with establishment of rapport with therapy team and/or safe exposure to psilocybin, e.g. suspected borderline personality disorder" added as a criterion for exclusion.

Consistent with our earlier report on the initial 12 patients from this trial (Carhart-Harris et al. 2016), transient anxiety lasting for minutes ($n = 15$) and headaches lasting no more than 1–2 days ($n = 8$) were the most common side effects. Five reported transient nausea but there were no cases of vomiting. Three reported transient paranoia within the duration of the acute drug experience but this was short-lived in every case. As with all our previous work with this compound, there were no reported cases of so-called flashbacks or persisting perceptual changes.

Fourteen patients reported visions of an autobiographical nature. In most cases, such visions were regarded as insightful and informative. One patient reported a vision of his father attempting to physically harm him when he was child,

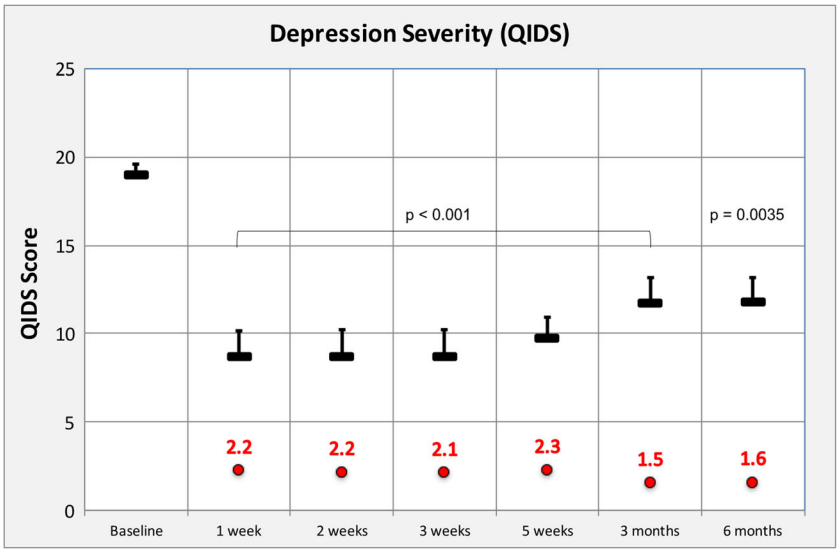

Fig. 1 Depression severity vs time: depression severity determined by the primary outcome measure, self-rated QIDS-SR16. Mean values were calculated for the 19 completers. Data are shown for the QIDS scores of 16–20 considered to reflect severe depression. All post-treatment assessments were obtained after the high-dose session, i.e. 1-week post-treatment refers to 1 week after the 25-mg psilocybin dose. Mean values are represented by the black horizontal bars with positive standard errors also included. 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 $p = 0.0035$. Patient 17's data is not included in the chart due to absent data points at 1 week to 4 months; however, his baseline and 6-month data is included in the text contained in "Results" section and retrospective ratings for 1 and 3 weeks post-treatment were also obtained and are reported in the text only

something he claimed not to have been previously conscious of. This patient subsequently felt confused about the authenticity of this putative memory and this was associated with a transient worsening of symptoms (see weeks 2 and 3 in fig. S1). Appealing to clinical equipoise, the study team felt it best practice not to make a judgement on the veridicality of this alleged memory but open and compassionate listening was maintained and the patient subsequently improved.

Suicidality scores on the QIDS-SR16 were significantly reduced 1 and 2 weeks post-treatment (mean reductions at week 1 = − 0.9, 95% CI = − 0.4 to − 1.4, $p < 0.002$; mean reduction at week 2 = − 0.85, 95% CI = − 0.4 to − 1.3, $p = 0.004$), with trend decreases at 3 (mean reduction = − 0.8, 95% CI = − 0.25 to − 1.3, $p = 0.01$) and 5 weeks (mean reduction = − 0.7, 95% CI = − 0.22 to − 1.2, $p = 0.01$). Scores on the suicide item of the HAM-D were significantly decreased 1-week post-treatment (mean reduction = − 0.95, 95% CI = − 0.58 to − 1.3, $p < 0.001$), with 16 of 19 patients scoring 0 at this time point and none showing an increase from baseline nor scoring the maximum on this measure. Scores on the genital/sexual dysfunction item of the HAM-D were also significantly reduced 1-week post-treatment (mean reduction = − 0.58, 95% CI = − 0.18 to − 0.98, $p = 0.002$) and no one scored the maximum nor showed an increase in sexual dysfunction from baseline.

The complete 11D-ASC scores can be found in the supplementary file. After Bonferroni correction (0.05/11 = 0.004), values for *experience of unity* (mean difference = 0.26, 95% CI = 0.12 to 0.41, $p = 0.001$), *spiritual experience* (mean difference = 0.28, 95% CI = 0.11 to 0.41, $p < 0.001$), *blissful state* (mean difference = 0.3, 95% CI = 0.16 to 0.44, $p < 0.001$), *insightfulness* (mean difference = 0.26, 95% CI = 0.11 to 0.41, $p < 0.001$) and *complex imagery* (mean difference = 0.18, 95% CI = 0.08 to 0.28, $p < 0.001$) were found to be significantly higher after 25 mg psilocybin than the 10-mg dose.

Previous work has indicated a strong relationship between the following 11D-ASC factors: experience of unity, spiritual experience and blissful state (Studerus et al. 2010); and a multiple correlation analysis confirmed their interrelatedness here ($r > 0.92$ for all permutations). We therefore decided to treat them as one factor (assigned the acronym 'USB'), taking mean values for each patient. Testing the hypothesis that this *USB* factor and *insight* would predict better clinical outcomes, we found significant relationships between mean scores of USB and insight (Fig. 2) during the 25-mg psilocybin experience and changes in QIDS-SR16 scores at 5 weeks ($r = - 0.49$, $p = 0.03$ and $r = - 0.57$, $p = 0.01$, respectively).

After the 6-month endpoint, information was collected on other treatments received by the patients (Watts et al. 2017). With the exception of patient 2 (who remained on venlafaxine throughout the trial and also received CBT shortly afterwards), no patients received additional treatments within 5 weeks of the 25-mg psilocybin dose. Six began new courses of antidepressant medication after the 3-month time point. Five received psychotherapy (CBT, psychodynamic, counselling and group therapy × 2) shortly before or after the 3-month

Table 2 Individual patient clinical ratings: clinical outcomes at various time points. The clinician administered ratings were completed at baseline and 1 week post-dosing only

	BDI				STAI			SHAPS			HAM-D		GAF	
	Baseline	1 week	3 months	6 months	Baseline	1 week	3 months	6 months	Baseline	1 week	3 months	Baseline	1 week	Baseline	1 week
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)	24.1 (5.4)	9.3 (7.6)	48.9 (10.3)	74.2 (16.05)
Difference vs baseline (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)		− 14.8 (7.8)		+ 25.3 (17.1)
Cohen's *d*		2.5	1.4	1.4		2.2	1.2	1.5		1.3	0.8		2.3		1.9
p value		$p < 0.001$	$p < 0.001$	$p < 0.001$		$p < 0.001$	$p < 0.001$	$p < 0.001$		$p < 0.001$	$p = 0.005$		$p < 0.001$		$p < 0.001$

period and five sought and successfully obtained psilocybin (without sanction from the study team) between 3 and 6 months. Removing the five that obtained psilocybin from the 3- and 6-month analyses did not substantially alter the main results: at 3 months, the effect size increased to 1.6 and the *p* value remained < 0.001; and at 6 months, the effect size increased to 1.7 and the *p* value became 0.018.

Assessing relapse at 6 months in responders (at 5 weeks) revealed only three of nine cases—with the remaining six maintaining response—even when using conservative criteria for relapse of QIDS score of 6+ or above at 6 months. These data tentatively imply that psilocybin may protect against relapse to an equivalent extent to daily use of an established antidepressant—as seen in discontinuation trials where responders either continue on medication (33% relapse) or transfer to placebo (46% relapse) for 6 months (Gueorguieva et al. 2017). Two major caveats here, however, are that one cannot reliably extrapolate from a sample of nine, and whereas patients in our trial received no interventions from us beyond the integration work done 1 week after their 25-mg psilocybin session, patients in clinical trials typically ingest a potentially active antidepressant daily for 6 months.

Discussion

This paper presents updated and extended data from an open-label clinical trial assessing psilocybin with psychological support for treatment-resistant depression. Findings corroborate our (Carhart-Harris et al. 2016) and others' previous results (Griffiths et al. 2016; Ross et al. 2016; Grob et al. 2011) supporting the safety and efficacy of psilocybin for depressive and anxiety symptoms. A fast and sustained response exceeding what might be expected from a placebo response was observed in many of the patients (see Carhart-Harris and Nutt (2016) for a relevant discussion). Notably, *all* 19 completers showed some reductions in the QIDS-SR16 scores at 1-week post-treatment and (nominally) maximal effects were seen at 5 weeks. Other interventions, not formally part of the present trial, confounded outcomes at 3 and 6 months, although safety was maintained and a sizeable proportion of the sample continued to demonstrate benefit (see Watts et al. (2017) for more details). Conclusions on efficacy are limited by the absence of a control condition in this trial, however.

Recent studies (Griffiths et al. 2016; Ross et al. 2016; Carhart-Harris et al. 2016), including the present one, help demonstrate the feasibility of treating patients with major depressive disorder with psilocybin plus psychological support. Two recent double-blind randomised control trials (RCTs) of psilocybin for depression and anxiety symptoms in a combined sample of 80 patients with life-threatening cancer found consistent safety and efficacy outcomes with those reported here (Griffiths et al. 2016; Ross et al. 2016). Only a subset of

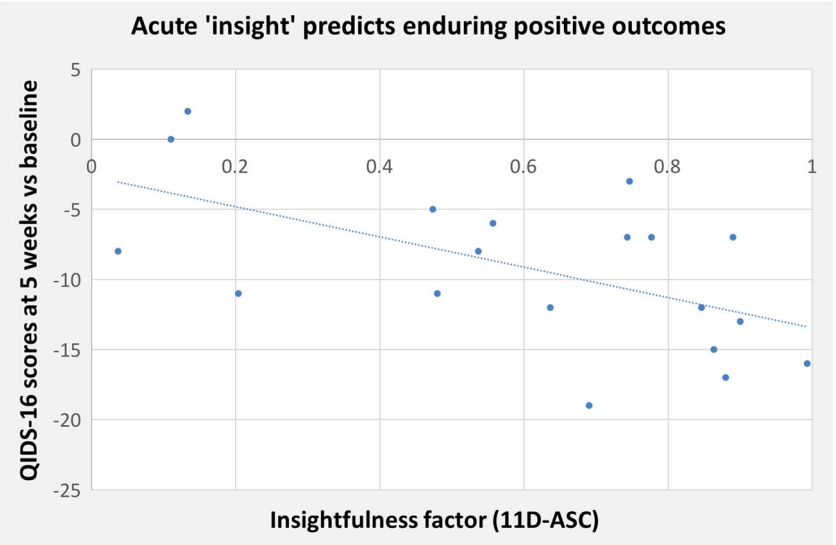

Fig. 2 Acute 'insight' measured by the 'insightfulness' factor of the 11D-ASC rated in the evening after the 25-mg psilocybin experience correlated significantly with reductions in depressive symptoms 5 weeks later ($r = -0.57$, $p = 0.01$, two-tailed)

patients recruited into these studies met the criteria for major depressive disorder however, and symptoms were not of the same severity as those seen here (i.e. mean baseline BDI scores were 18.1 and 16 in the Griffiths et al. and Ross et al. studies, respectively, whereas they were 35 in the present study). A comprehensive RCT designed to properly assess psilocybin's efficacy for major depressive disorder, with some form of placebo control, is therefore warranted (Carhart-Harris and Goodwin 2017).

Regarding mechanisms, we recently proposed a model by which psychedelic-induced 5-HT2AR signalling rapidly induces an acute state of plasticity in which an enriched context (Carhart-Harris et al., in review) may lead to cognitive biases being revised (Carhart-Harris and Nutt 2017; Carhart-Harris and Goodwin 2017)—see also Branchi (2011). The above-reported correlation between acute 'insightfulness' and enduring reductions in depressive symptoms may be viewed as broadly supportive of this model. Moreover, recently published fMRI data collected as part of the present trial may help to develop and refine this model (Roseman et al., in review; Carhart-Harris et al., in review).

Future research should endeavour to better characterise, control and measure the various psychological components contained within the current psychedelic treatment model. There is an assumption that individuals under the influence of a psychedelic are especially sensitive to the *context* in which the experience occurs, both in terms of (1) prior expectations and other relevant state and trait factors and (2) environmental factors, e.g. the quality of the relationships with persons attending to them before, during and after the experience and patients' relationship to the music listened to during the sessions (Kaelen et al. 2015)—and this matter has recently been discussed in length (Carhart-Harris et al., in review). In order to properly assess the relative contribution of these variables and their assumed interactions with psilocybin, it will be necessary to properly control and measure them, and this has presently not yet been done to a satisfactory level (see Carhart-Harris et al. (in review) for suggestions on how this might be done).

Relatedly, psychotherapeutic models used to support and mediate the psilocybin experience need to be better defined, tested and potentially manualised. Basic principles for safe therapeutic work with psychedelics can be found in guidelines (Johnson et al. 2008) and books (Richards 2015) but more systematic verification, refinement and (eventual) manualisation of treatment approaches are needed for subsequent roll-out (Carhart-Harris and Goodwin 2017). Moreover, cost-effectiveness will become increasingly salient as the development of psilocybin as a treatment model progresses. The major qualifier here is that experiments intended to evaluate the contribution of psychological variables to the psychedelic experience need to be conceived and conducted with an appreciation of the special vulnerability of individuals under the influence of psychedelics (again, see Carhart-Harris et al. (in review). Thus, certain standards of care, including a certain level of psychological support, may be non-negotiable if safety is to be maintained.

An obvious limitation of the present study is its open-label design and absence of a control condition. The initial plan was to conduct a placebo-controlled RCT but regulatory and drug procurement challenges meant that available resources could only support a smaller trial. The present results may be viewed as a successful demonstration of proof-of-principle, however, supporting the view that psilocybin can be given safely, even in severe cases of depression, with the caveat that appropriate control of context (e.g. the provision of psychological support and a comfortable environment) is essential for positive outcomes (Carhart-Harris et al., in review). Impressions of efficacy gleaned from the present study's findings may be cautiously described as 'promising'—and if supported by larger

and better controlled trials, psilocybin's low toxicity, favourable side effect profile and putative rapid and enduring antidepressant action could render it at least competitive with currently available treatments for major depression, whose therapeutic actions may be either delayed, e.g. in the cases of SSRIs and psychotherapy, or short-lived, e.g. in the case of ketamine. Comparative efficacy trials may therefore be an interesting next step. Such designs may also have merit in terms of addressing the challenge of maintaining the study blind in trials with psychedelics (Carhart-Harris and Goodwin 2017).

Another limitation of the present trial is that the final eight patients were all male. This is regretful as it limits extrapolation to the general population, where rates of treatment-resistant depression may be marginally higher in women than in men (Kubitz et al. 2013). Greater effort will be made in future trials to recruit more representative samples of the target population. Another limitation deserving of mention is the issue of assessing duration of current depressive episode. Patients gave estimates based on the question "For how long has your current depression lasted?" but some chose to estimate based on the duration of their chronic illness, believing they had not experienced a discernable remission for years–decades, even during periods when their symptoms were relatively less severe.

In summary, we have presented updated and extended data from a feasibility trial assessing psilocybin with psychological support for treatment-resistant depression. With the caveat that this was an open-label trial with no control condition, safety and efficacy outcomes continue to support the case for further research (Carhart-Harris and Goodwin 2017). Identifying key psychological and pharmacological variables comprising the treatment model, and testing their assumed interactions, is one of a number of important next steps (Carhart-Harris et al., in review).

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

Long-term follow-up of psilocybin-facilitated smoking cessation

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ABSTRACT

Background: A recent open-label pilot study ($N = 15$) found that two to three moderate to high doses (20 and 30 mg/70 kg) of the serotonin 2A receptor agonist, psilocybin, in combination with cognitive behavioral therapy (CBT) for smoking cessation, resulted in substantially higher 6-month smoking abstinence rates than are typically observed with other medications or CBT alone. *Objectives*: To assess long-term effects of a psilocybin-facilitated smoking cessation program at ≥12 months after psilocybin administration. *Methods*: The present report describes biologically verified smoking abstinence outcomes of the previous pilot study at ≥12 months, and related data on subjective effects of psilocybin. *Results*: All 15 participants completed a 12-month follow-up, and 12 (80%) returned for a long-term (≥16 months) follow-up, with a mean interval of 30 months (range = 16–57 months) between target-quit date (i.e., first psilocybin session) and long-term follow-up. At 12-month follow-up, 10 participants (67%) were confirmed as smoking abstinent. At long-term follow-up, nine participants (60%) were confirmed as smoking abstinent. At 12-month follow-up 13 participants (86.7%) rated their psilocybin experiences among the five most personally meaningful and spiritually significant experiences of their lives. *Conclusion*: These results suggest that in the context of a structured treatment program, psilocybin holds considerable promise in promoting long-term smoking abstinence. The present study adds to recent and historical evidence suggesting high success rates when using classic psychedelics in the treatment of addiction. Further research investigating psilocybin-facilitated treatment of substance use disorders is warranted.

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Hallucinogen; tobacco; smoking cessation; nicotine; addiction; psilocybin; psychedelic; mystical experience; spirituality

Introduction

With almost 6 million tobacco-related deaths per year worldwide, and that number projected to rise to an estimated 8 million annual mortalities by 2030, smoking remains among the leading public health concerns of the 21st century (1). At present, the most successful available smoking cessation treatments fail to promote long-term abstinence in the majority of individuals who use them (2,3), underscoring an urgent need to explore innovative treatment approaches.

The authors recently reported on a novel intervention for smoking cessation combining two to three administrations of psilocybin, a naturally occurring serotonin 2A receptor (5-HT2AR) agonist, with CBT. Initial results showed that 80% of participants in this open-label pilot study ($N = 15$) were biologically verified as smoking abstinent at the 6-month follow-up (4). Pilot results demonstrated safety and feasibility in this sample, with physiological adverse effects limited to mild post-session headache, and modest acute elevations in blood pressure and heart rate (4). Six volunteers (40%) reported acute challenging (i.e., fearful, anxiety-provoking) psilocybin session experiences. However, these effects resolved by the end of drug session days via interpersonal support from study staff, without pharmacologic intervention or persisting deleterious sequelae (4). The current report presents long-term follow-up data from this trial, including abstinence outcomes at 12 months and an average of 30 months post-treatment, as well as data on persisting psychological effects at 12-month follow-up.

Methods

This study was approved by the Institutional Review Board of Johns Hopkins Medicine, and all participants provided informed consent. Participants were 15 smokers (10 males) without histories of severe mental illness, with a mean age of 51 years, who smoked on average 19 cigarettes per day (CPD) for a mean of 31 years at screening, with a mean of six previous quit attempts. Participants underwent a 15-week combination treatment consisting of four weekly preparatory meetings integrating CBT, elements of mindfulness training, and guided imagery for smoking cessation.

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Participants received a moderate (20 mg/70 kg) dose of psilocybin in week 5 of treatment, which served as the target-quit date (TQD), and a high dose of psilocybin (30 mg/70 kg) approximately 2 weeks later. Participants had the opportunity to participate in a third, optional high-dose psilocybin session in week 13 of study treatment.

For 10 weeks following the TQD, participants returned to the laboratory to provide breath and urine samples to test for recent smoking, complete self-report questionnaires, and meet with study staff. Participants returned for follow-up meetings at 6 and 12 months post-TQD, and were later invited back for a retrospective interview probing potential mechanisms of the study treatment at a mean of 30 months post-TQD. For a detailed description of the study sample and intervention see Johnson et al. (4). The current report presents previously unpublished data regarding smoking cessation outcomes at the 12-month and long-term follow-ups.

Measures

Smoking biomarkers

Biomarkers of recent smoking were used to assess participants' smoking status at 12-month and long-term follow-ups. Breath carbon monoxide (CO) was measured using a Bedfont Micro+ Smokerlyzer (Haddonfield, NJ). Urine samples were collected and sent to an independent laboratory (Friends Medical Laboratory, Baltimore, MD) for analysis of cotinine, a metabolite of nicotine.

Timeline follow-back (TLFB)

Using the TLFB, a widely used retrospective measure of substance use (5), participants provided self-reported estimates of their daily cigarette consumption in the 30 days prior to beginning the study treatment. On all subsequent visits participants self-reported daily cigarette consumption since the last laboratory visit using the TLFB. Therefore, the TLFB provided continuous daily data on cigarette consumption.

Persisting effects questionnaire

Participants completed a 143-item questionnaire designed to measure persisting changes in attitudes, moods, behavior, and spirituality attributed to their most recent psilocybin experience 1 week after each psilocybin session. A retrospective version of this questionnaire was administered at the 12-month follow-up asking participants to respond regarding their cumulative psilocybin session experiences.

This questionnaire has previously been used to assess intermediate and long-term effects of psilocybin (6–8). The initial 140 items are rated on a 6-point scale ranging from 0 (*none*) to 5 (*extreme*) assessing positive and negative changes in six categories: Attitudes about life (26 items); Attitudes about self (22 items); Mood changes (18 items); Relationships (18 items); Behavioral changes (two items); and Spirituality (43 items). Additionally, this questionnaire included three items asking participants to rate: (1) the overall personal meaning, (2) spiritual significance, and (3) effects on well-being or life satisfaction attributed to psilocybin experiences or contemplation of those experiences.

Mystical experience questionnaire (MEQ30)

The MEQ30 is a validated 30-item scale designed to assess the occurrence and intensity of mystical-type experiences occasioned by psilocybin (9,10). Psilocybin occasioned mystical experiences are defined by acute feelings of unity, sacredness, a noetic quality, positive mood, transcendence of space/time, and ineffability (6), and have previously shown a significant association with successful psilocybin-facilitated smoking cessation outcomes at 6-month follow-up (11). The MEQ30 was completed at the conclusion of each psilocybin session approximately 7 hours after drug administration. Participants responded based on their experience during each particular session day.

Data analysis

Participants were judged abstinent if breath CO value was ≤6 ppm (12), urinary cotinine was <200 ng/mL (13), and if no smoking was reported on the TLFB for the previous 7 days. Urine samples testing negative for recent smoking were scored as 0 ng/mL for all analyses, as laboratory results did not provide specific values for negative (<200 ng/mL) samples. Participants who did not report to a follow-up visit were considered to have smoked. The three participants who did not complete a long-term follow-up (which occurred at a mean of 30 months post-TQD for those who completed) had been confirmed as daily smokers at the 12-month follow-up. Thus, for these three individuals, carbon monoxide, urine cotinine, and TLFB self-reported daily smoking data for the long-term follow-up were imputed using their individual 12-month follow-up values.

Repeated measures ANOVA tested for changes in TLFB self-reported smoking from study intake to long-term follow-up. Planned comparison two-tailed paired *t*-tests were used to compare TLFB data between study intake and each of the following time points: end of treatment (10 weeks post-TQD), and 6-month, 12-month, and long-term follow-ups.

Descriptive statistics were calculated using Persisting Effects Questionnaire data to assess long-term positive and negative changes, personal meaning, and spiritual significance attributed to psilocybin session experiences one week after each session, and at 12-months post-TQD.

To examine the hypothesis that greater mystical-type effects and more positive attributions regarding psilocybin sessions would be associated with greater smoking cessation success, Pearson's correlations were calculated between psilocybin session ratings (i.e., individuals' mean MEQ30 score across psilocybin sessions from the end of each session day, and individuals' mean ratings of personal meaning and spiritual significance across psilocybin sessions from one week after each session) and long-term change scores on each smoking-related measure (i.e., breath CO, cotinine, TLFB). Change scores were calculated as each participant's score at study intake subtracted from that participant's score at long-term follow-up. For the TLFB this was calculated as mean CPD in the 30 days preceding study intake, subtracted from mean CPD from TQD to long-term follow-up. All datasets examined via correlational analyses were normally distributed as determined by Dallal–Wilkinson–Lilliefor corrected Kolmogorov–Smirnov tests at an alpha level of 0.05 (14).

Results

All 15 participants completed a 12-month follow-up. Twelve (80%) returned for a long-term follow-up (mean 30 months post-TQD; range = 16–57 months) and provided data regarding current smoking and past treatment experience. At 12-month follow-up, 10 participants (67%) were biologically confirmed as smoking abstinent, with 8 of these participants reporting continuous abstinence since their TQD. At long-term follow-up, nine participants (60%) were biologically confirmed as smoking abstinent, with 7 of these participants reporting continuous abstinence since their TQD (Figure 1A–C).

Repeated measures ANOVA found significant change in self-reported smoking on the TLFB from study intake through the four follow-up time points at 10 weeks, 6 months, 12 months, and a mean of

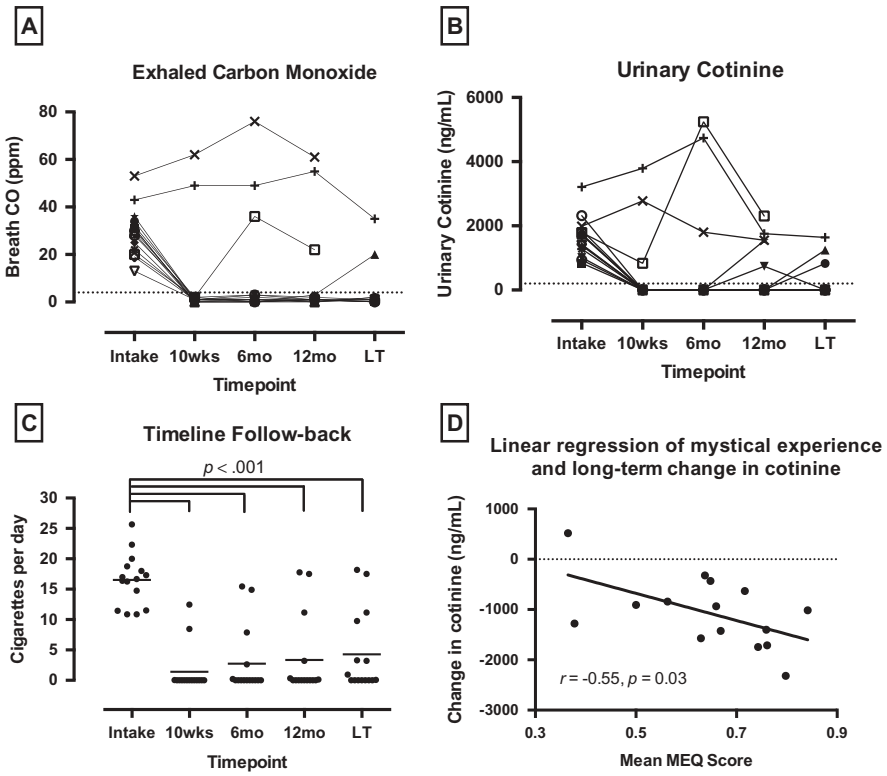

Figure 1. (A) Exhaled carbon monoxide (CO) shown for each participant from baseline through long-term follow-up (LT). (B) Urine cotinine levels shown for each participant from baseline through long-term follow-up. (C) Timeline follow-back (TLFB) data of self-reported daily smoking; individual data points show individual participant data, with the group mean indicated by horizontal line; horizontal brackets indicate significant reductions between intake and each of four follow-up assessments (2-tailed paired *t*-tests, $p < 0.001$). (D) Relationship between average scores on the Mystical Experience Questionnaire (MEQ30) at the conclusion of each psilocybin session, and change in urinary cotinine levels from study intake to long-term follow-up. Data points show data from each of the 15 individual participants with best-fit linear regression.

30 months post-TQD ($F_{2,23} = 81.4$; $p < 0.001$). Planned comparison two-tailed paired t-tests showed a significant decrease in self-reported daily smoking between study intake and the four follow-up time points, from a mean (SD) of 16.5 (4.3) CPD at study intake, to 1.4 (3.8) CPD at 10 weeks ($t_{14} = 19.4$, $p < 0.001$); 2.7 (5.5) CPD at 6 months ($t_{14} = 11.6$, $p < 0.001$); 3.3 (6.5) CPD at 12 months ($t_{14} = 9.2$, $p < 0.001$); and 4.3 (6.6) CPD at long-term follow-up ($t_{14} = 9.1$, $p < 0.001$).

Positive persisting effects were rated higher than negative persisting effects across all six domains of the Persisting Effects Questionnaire, with average negative effects scores ranging from 3.2 to 8.1% of maximum possible score, and average positive effects scores ranging from 53 to 64% of maximum possible score (Table 1). For the final question regarding effects on well-being or life satisfaction attributed to psilocybin experiences or contemplation of those experiences, one participant deviated from instrument instructions by endorsing both−3 (decreased very much) and +3 (increased very much) at the 12-month follow-up. We therefore excluded this person's data on this single item from the results reported in Table 1. No other participants endorsed any level of decrease in well-being or life satisfaction related to psilocybin session experiences at the 12-month follow-up.

The participant endorsing mixed results for well-being or life-satisfaction at the 12-month follow-up attributed the decrease in well-being or life-satisfaction to psilocybin session content in which she reported re-experiencing traumatic childhood memories. This individual was referred to additional counseling, which she reported to be helpful in integrating these experiences and resolving associated difficulty. One other participant sought outside counseling after their psilocybin session experiences, although this was reportedly undertaken with the intention of personal growth and self-improvement. Consistent with previously published data (4), no participants reported an increase in bothersome visual disturbances at the 12-month follow-up relative to baseline, and no clinically significant psychological sequelae were spontaneously reported at the long-term follow-up.

Participants attributed great personal meaning and spiritual significance to their psilocybin experiences at 12-months post-TQD, with 13 (86.7%) rating these experiences among the five most personally meaningful of their lives, and 13 (86.7%) rating them among the five most spiritually significant experiences of their lives.

Changes in urine cotinine levels from study intake to long-term follow-up were significantly correlated with mean ratings of personal meaning of psilocybin session from 1 week after each session ($r = -0.55$, $p = 0.04$), and mean MEQ30 scores from the end of each session day ($r = -0.55$, $p = 0.03$; Figure 1D). The seven other correlations between psilocybin session attributes and smoking cessation success did not reach significance

Table 1. Persisting effects questionnaire ratings at 1 week after each psilocybin session, and 12 months after psilocybin session 1.*

Subscale/item	Mean (SEM) Session 1	Mean (SEM) Session 2	Mean (SEM) Session 3[a]	Mean (SEM) 12 months
Positive attitudes about life	49.3 (6.5)	63.2 (4.2)	69.7 (6.0)	63.5 (5.9)
Negative attitudes about life	10.4 (3.2)	6.3 (1.4)	5.5 (1.4)	7.0 (2.8)
Positive attitudes about self	42.2 (6.6)	57.7 (5.2)	65.3 (5.8)	60.5 (5.8)
Negative attitudes about self	10.4 (2.4)	6.1 (1.3)	6.1 (1.3)	8.1 (3.1)
Positive mood changes	34.6 (6.0)	53.5 (5.8)	62.0 (8.4)	53.0 (6.4)
Negative mood changes	14.1 (5.4)	4.4 (1.9)	5.4 (4.5)	7.0 (3.6)
Altruistic/positive social effects	34.9 (7.8)	56.3 (6.0)	62.2 (7.1)	57.6 (6.2)
Antisocial/negative social effects	3.5 (1.7)	2.8 (1.7)	3.7 (2.2)	6.5 (2.6)
Positive behavior changes	52.9 (9.3)	65.3 (7.9)	80.0 (4.9)	64.0 (6.8)
Negative behavior changes	7.1 (5.0)	0.0 (0.0)	3.3 (2.3)	4.0 (4.0)
Increased spirituality	40.0 (7.4)	55.1 (6.0)	60.5 (7.1)	55.2 (6.6)
Decreased spirituality	3.4 (1.3)	1.2 (0.6)	1.0 (0.5)	3.2 (1.6)
How personally meaningful was the experience? (score range: 1–8)[b]	5.4 (0.5)	6.3 (0.2)	6.3 (0.3)	7.0 (0.2)
How spiritually significant was the experience? (score range: 1–6)[c]	3.4 (0.4)	4.2 (0.2)	4.4 (0.4)	5.1 (0.3)
Did the experience change your sense of well-being or life satisfaction? (score range: −3 to +3)[d]	1.4 (0.5)	2.5 (0.2)	2.7 (0.3)	2.1 (0.3)

*Data are mean scores with 1 SEM shown in parentheses ($N = 15$); data on attitudes, mood, altruistic/social effects, and behavior changes are expressed as percentage of maximum possible score; data for the final three questions are raw scores.

[a]For Session 3 scores $N = 12$, as three participants declined an optional third psilocybin session.

[b]Rating scale: 1 = no more than routine, everyday experiences. 2 = similar to meaningful experiences that occur on average once or more a week. 3 = similar to meaningful experiences that occur on average once a month. 4 = similar to meaningful experiences that occur on average once a year. 5 = similar to meaningful experiences that occur on average once every 5 years. 6 = among the 10 most meaningful experiences of my life. 7 = among the 5 most meaningful experiences of my life. 8 = the single most meaningful experience of my life.

[c]Rating scale: 1 = not at all. 2 = slightly. 3 = moderately. 4 = very much. 5 = among the 5 most spiritually significant experiences of my life. 6 = the single most spiritually significant experience of my life.

[d]Rating scale: −3 = decreased very much. −2 = decreased moderately. −1 = decreased slightly. 0 = no change. 1 = increased slightly. 2 = increased moderately. 3 = increased very much.

(p range: 0.10 to 0.36) but were consistently in the predicted direction with moderate effect sizes (r range: −0.25 to −0.44).

Discussion

These results, together with previously reported findings, indicate that psilocybin may be a feasible adjunct to smoking cessation treatment. In controlled studies, the most effective smoking cessation medications typically demonstrate less than 31% abstinence at 12 months post-treatment (15,16), whereas the present study found 60% abstinence more than a year after psilocybin administration. However, the current findings are limited by the small sample, open-label design, and lack of control condition, which preclude making definitive conclusions about efficacy. Furthermore, participant self-selection bias may have played a role in observed success rates, as the study enrolled only individuals motivated to quit and willing to undergo a time-intensive experimental treatment for no monetary compensation.

Additional, carefully controlled research in larger, more diverse samples is necessary to determine efficacy. Toward this end, the authors are currently conducting a randomized comparative efficacy trial in a larger study sample (ClinicalTrials.gov Identifier NCT01943994). This study is evaluating smoking cessation outcomes between individuals receiving a single high dose (30 mg/70 kg) of psilocybin vs. a standard 8- to 10-week course of nicotine replacement therapy (i.e., patch), with both groups receiving the same cognitive behavioral smoking cessation intervention.

Nevertheless, the present results suggest persisting effects of psilocybin-facilitated treatment well beyond the time course of acute drug action. Consistent with previous findings, results indicated greater mystical-type effects and more positive attributions regarding psilocybin sessions were associated with greater smoking cessation success. The only significant correlations were between cotinine reductions and mystical-type psilocybin effects, and between cotinine reductions and ratings of session personal meaning. However, all other correlations between subjective effects of psilocybin and change in smoking-related measures were in the predicted direction with a moderate effect size. Therefore, the failure of these other correlations to reach significance might constitute a type II error related to small sample size.

While the intervention used in this study was not explicitly "spiritual" in nature, participants consistently attributed a high degree of spiritual significance to their psilocybin session experiences, raising questions about the role of spirituality in smoking cessation. Several studies suggest that increased levels of spirituality are associated with improved treatment outcomes in substance dependence recovery (17–20), and pilot survey data indicate that 78% of smokers reported that spiritual resources would be helpful in quitting smoking (21). The lasting psychological and behavioral shifts observed following psychedelic administration may be mediated in part by the salient, often subjectively positive acute effects of 5-HT2AR agonists, which have sometimes been characterized as mystical or transcendent (7,11,22).

Combined with historical data suggesting high success rates of psychedelic-facilitated treatment of alcoholism approximately doubling the odds of success at initial follow-up (23), and promising recent pilot data on psilocybin-facilitated treatment of alcohol dependence (24), the present findings indicate that 5-HT2AR agonists may hold therapeutic potential in treating a variety of substance use disorders in the context of a structured treatment program. Considering the often chronic and intractable nature of addictive disorders, further investigation of psychedelic-facilitated treatment of addiction and underlying neurobiological mechanisms represent important future directions for research.

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Declaration of interest

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Original Paper

Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study

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Abstract

Several lines of evidence suggest that classic (5HT2A agonist) hallucinogens have clinically relevant effects in alcohol and drug addiction. Although recent studies have investigated the effects of psilocybin in various populations, there have been no studies on the efficacy of psilocybin for alcohol dependence. We conducted a single-group proof-of-concept study to quantify acute effects of psilocybin in alcohol-dependent participants and to provide preliminary outcome and safety data. Ten volunteers with DSM-IV alcohol dependence received orally administered psilocybin in one or two supervised sessions in addition to Motivational Enhancement Therapy and therapy sessions devoted to preparation for and debriefing from the psilocybin sessions. Participants' responses to psilocybin were qualitatively similar to those described in other populations. Abstinence did not increase significantly in the first 4 weeks of treatment (when participants had not yet received psilocybin), but increased significantly following psilocybin administration ($p < 0.05$). Gains were largely maintained at follow-up to 36 weeks. The intensity of effects in the first psilocybin session (at week 4) strongly predicted change in drinking during weeks 5–8 ($r = 0.76$ to $r = 0.89$) and also predicted decreases in craving and increases in abstinence self-efficacy during week 5. There were no significant treatment-related adverse events. These preliminary findings provide a strong rationale for controlled trials with larger samples to investigate efficacy and mechanisms.

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Keywords

Addiction treatment, alcoholism, hallucinogens, psilocybin, clinical trial, motivational interviewing

Introduction

In the 1950s through early 1970s there was extensive research on the use of LSD and other classic (5HT2A agonist or partial agonist) hallucinogens in the treatment of addiction (Abuzzahab and Anderson, 1971; Dyck, 2006; Grinspoon and Balakar, 1997; Halpern, 1996; Mangini, 1998), existential distress in dying patients (Grof et al., 1973; Pahnke et al., 1969; Richards, 1975; Richards et al., 1977), pain (Kast, 1966; Kast and Collins, 1964), and other conditions (Grinspoon and Balakar, 1997; Grof, 2008). A recent meta-analysis (Krebs and Johansen, 2012) examined the six published randomized trials (Bowen et al., 1970; Hollister et al., 1969; Ludwig et al., 1969; Pahnke et al., 1970; Smart et al., 1966; Tomsovic and Edwards, 1970) of LSD treatment of alcoholism. A total of 325 participants received active treatment with LSD, and 211 received control treatment. At the first post-treatment follow-up (ranging from 1 month to 12 months) the odds ratio for improvement was 1.96, favoring LSD (95% confidence interval 1.36–2.84, $Z = 3.59$, $p = 0.0003$).

The past decade has seen a rapid growth of interest in potential clinical applications of the classic hallucinogen psilocybin (Bogenschutz, 2012; Burdick and Adinoff, 2013; Carhart-Harris et al., 2012, 2013; Garcia-Romeu et al., 2013; Grob et al., 2011; Kometer et al., 2012; Nichols, 2014). Using a double-blind, cross-over design, Grob et al. administered psilocybin 0.2 mg/kg vs. placebo to 12 patients with anxiety related to advanced cancer (Grob et al., 2011). Participants showed significant improvement with time, and there were statistical trends suggesting a positive effect of psilocybin on mood. Additional clinical trials in cancer patients are currently nearing completion at Johns Hopkins University and New York University (Nichols, 2014). A recent pilot study of psilocybin as an adjunct in smoking cessation treatment resulted in remarkable rates of abstinence (80% point abstinence at 6-month follow-up) (Johnson et al., 2014). Extensive clinical research with the classic hallucinogens (LSD, psilocybin, DMT, mescaline) has established their relative safety within a clinical research setting when subjects are carefully screened, supervised, and followed up (Strassman, 1984). A number of articles and chapters have reviewed the literature on the use of hallucinogens in the treatment of addictions (Abuzzahab and Anderson, 1971; Dyck, 2006; Grinspoon and Balakar, 1997; Halpern, 1996; Mangini, 1998), with the recent addition of two reviews that incorporate current research on the effects of classic hallucinogens more generally and discuss possible mechanisms of action (Bogenschutz and Pommy, 2012; Ross, 2012).

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Biological mechanisms

Although classic hallucinogens bind to many serotonin receptor subtypes and other receptors (Ray, 2010), the psychoactive effects of all classic hallucinogens appear to depend primarily on their actions at 5HT2A receptors (Nichols, 2004; Vollenweider and Kometer 2010; Vollenweider et al., 1998). Administration of classic hallucinogens in rat models has been shown to induce down-regulation of 5HT2A receptors, particularly those in the anterior cingulate and frontomedial cortex, likely accounting for the rapid development and reversal of behavioral tolerance to most classic hallucinogens (Buckholtz et al., 1990; Gresch et al., 2005).

The behavioral correlates and effects of 5HT2A receptor activity are complex. Increased 5HT2A receptor binding has been found in relation to pathological conditions in humans including depression (Shelton et al., 2009), impulsive aggression (Rosell et al., 2010), neuroticism (Frokjaer et al., 2008), borderline personality disorder (Soloff et al., 2007), and suicide (Anisman et al., 2008). The relationship of 5HT2A receptor binding/activity and alcoholism or alcohol exposure is less clear. Family history of alcoholism may be associated with lower 5HT2A binding (Underwood et al., 2008), and alcoholism is not consistently associated with change in 5HT2A receptor levels (Thompson et al., 2012; Underwood et al., 2008). Among alcoholics, one small post-mortem study reported that higher impulsivity was associated with increased 5HT2A receptor binding (Thompson et al., 2012). In animal models, alcohol exposure has been associated with region-specific increases (Akash et al., 2008) and decreases (George et al., 2010) in 5HT2A receptors binding. Studies indicate that increased activity in 5HT2A-mediated pathways relative to 5HT2C activity increases cue response and impulsivity in rat models of cocaine addiction (Cunningham and Anastasio, 2014). 5HT2A antagonists suppress alcohol consumption in animal models (Johnson, 2008). However, two large trials of the 5HT2A antagonist ritanserin failed to demonstrate beneficial effects in people with alcohol dependence (Johnson et al., 1996; Wiesbeck et al., 1999).

Animal studies suggest mechanisms by which acute activation of 5HT2A receptors could activate intracellular signaling pathways resulting in persisting changes in cellular structure and synapses. The classic hallucinogen DOI increases expression of glial cell line-derived neurotrophic factor (GDNF) mRNA in glioiblastoma cells by a 5HT2A-dependent mechanism (Tsuchioka et al., 2008). Through its action on 5HT2A receptors, DOI has also been shown to increase levels of mRNA for brain-derived neurotrophic factor (BDNF) in rat parietal cortex and other neocortical regions, with decreases in the hippocampus and no change in piriform cortex (Vaidya et al., 1997). These findings are relevant because levels of BDNF and GDNF are inversely related to alcohol consumption and conditioned place preference in animal models (Ghitza et al., 2010). DOI activates intracellular signaling cascades associated with dendritic spine remodeling on rat pyramidal cells, and transiently increases the size of dendritic spines on cortical neurons (Jones et al., 2009).

Psychological models of psychedelic treatment

Clinical work with classic hallucinogens has emphasized the central role of the altered state of consciousness experienced during the drug's acute effects (Grof, 2008; Hoffer, 1967; Masters and Houston, 2000; Pahnke et al., 1970; Sherwood et al., 1962). The "psycholytic" model of treatment emphasized the use of classic hallucinogens to enhance the process of psychodynamic psychotherapy by making unconscious material more accessible (Leuner, 1967). The "psychedelic" treatment model on the other hand emphasized the use of relatively high doses of classic hallucinogens (usually LSD) to occasion a "peak-psychedelic" or mystical experience of ego loss, often likened to psychological death and rebirth (Kurland et al., 1967). The latter model was used in most of the clinical studies conducted in North America using LSD in the treatment of addiction or existential anxiety in the dying. The concept of a singular transformative experience leading to lasting behavior change is consistent with classic descriptions of religious conversion (James, 1902), "spiritual awakening" in the context of Alcoholics Anonymous (Forcehimes, 2004), and spontaneous Quantum Change experiences (Miller and C'de Baca, 2001). Recent studies have demonstrated that the self-reported "mystical" dimension of the psilocybin experience (feelings of unity, sacredness, ultimate reality, transcendence of time and space, deeply felt positive mood, and ineffability (Pahnke, 1963)) significantly predicts the lasting personal significance of the experience (Griffiths et al., 2008) and personality change (Maclean et al., 2011) in normal volunteers receiving psilocybin.

The evidence summarized above provides a convincing rationale for investigating whether a classic hallucinogen can improve treatment response among patients with alcohol dependence. In spite of the accumulating evidence that psilocybin has clinically relevant effects and is safe under controlled conditions, there are no prior studies of psilocybin in the treatment of alcohol dependence. We therefore undertook a proof-of-concept study which aimed to quantify the psychoactive effects and tolerability of oral psilocybin in alcohol-dependent participants, and to evaluate outcomes during and after completion of treatment.

Methods

Study design

The study employed a single-group, within-subjects design. Participants received a 12-week, 14-session manualized intervention including two open-label psilocybin sessions in which psilocybin was administered: the first after 4 weeks of psychosocial treatment, the second after 8 weeks. Outcome data were collected for a total of 36 weeks.

Participants

Participants were recruited from the community using advertisements in local media and flyers. They were males and females age 25–65 with a diagnosis of active alcohol dependence, ascertained using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1996), and at least two heavy drinking days in the past 30 days, who were concerned about their drinking and not currently in treatment. Participants were excluded if screening showed them to have exclusionary medical or psychiatric conditions; family history of schizophrenia, bipolar disorder, or suicide; cocaine, psychostimulant, or opioid dependence; or history of using hallucinogens more than 10 times (or any use in the past 30 days). Participants were required to be abstinent and not in alcohol withdrawal at the time of the psilocybin sessions.

Participants provided written informed consent, and all study procedures were reviewed and approved by the IRB of the University of New Mexico Health Sciences Center.

Interventions

Psychosocial intervention. The psychosocial intervention comprised a total of 12 sessions: seven sessions of Motivational Enhancement Therapy (MET: a structured approach using the principles of motivational interviewing (Miller and Rolnick, 2013)), three preparation sessions, and two debriefing sessions. Four sessions occurred before the first psilocybin session, four sessions between the first and second psilocybin sessions, and four sessions after the second psilocybin session. The psychosocial intervention was conducted by a team of two therapists. One performed the seven MET sessions focused on changing drinking behavior, while the other was responsible for preparation before, support during, and debriefing after the psilocybin sessions. Both therapists were present for the preparation and debriefing sessions, as well as the psilocybin sessions. Three of the authors (MB, AF, CW) served as study therapists. Therapy sessions were audiorecorded. The first and third MET sessions were coded using the Motivational Interviewing Treatment Integrity (MITI 3.1) coding system (Moyers et al., 2005) by a rater trained to reliability.

Dosing and administration of study medications. On the morning of the psilocybin sessions, participants were required to be afebrile, non-hypertensive, non-tachycardic, abstinent from alcohol for at least 24 hours, and without evidence of alcohol withdrawal. Urine drug screens were negative for cocaine, psychostimulants, and opioids, and breath was negative for alcohol. The psilocybin sessions took place in a room that was specially prepared to provide a living-room-like environment for the sessions. Individualized doses of psilocybin (based on participant weight) were prepared by the study pharmacist on the morning of the session, and placed in a single gelatin capsule. Participants ingested the psilocybin capsule followed by 4 ounces of water. They were instructed to lie on a couch wearing eyeshades and headphones (providing a standardized program of music), and to direct their attention toward their internal experience. Participants remained under observation for at least 8 hours following psilocybin administration. Both therapists were present throughout the session. Interactions with the participants were supportive and non-directive. Medications were available for administration if needed to treat hypertension (sublingual nitroglycerin 0.4 mg), anxiety (lorazepam 1–2 mg PO/IM), or acute psychosis (ziprasidone 10–20 mg PO/IM). Beginning 7 hours after drug administration, participants completed questionnaires and assessments, and a brief clinical interview was performed, including mental status exam. Participants were escorted home at the end of the session by a family member or friend, who stayed with the participant overnight.

For the first psilocybin session, participants received a dose of 0.3 mg/kg. For the second session, the dose was increased to 0.4 mg/kg unless the participant (i) was unwilling to increase the dose; (ii) experienced adverse effects during the first session which suggested that a higher dose would pose significant risk; or (iii) reported a "complete" mystical experience during the first session (Griffiths et al., 2006), indicating very strong effects from 0.3 mg/kg.

Assessments

Medical evaluation. Medical screening consisted of medical history and physical examination, ECG, liver function tests, complete blood count, blood chemistries, urinalysis, serum pregnancy test, and body mass index. Women of childbearing potential completed a menstrual calendar at each assessment visit, and urine pregnancy tests were completed prior to each drug administration session. The Clinical Institute Withdrawal Scale—Alcohol, revised (CIWA-Ar) (Sullivan et al., 1989) was used to assess alcohol withdrawal at screening and before the psilocybin sessions.

Psychiatric and substance use disorder diagnoses. The SCID (First et al., 1997) was used to diagnose DSM-IV Axis I disorders including substance abuse and dependence diagnoses.

Acute hallucinogen effects. Self-report scales (administered 7 hours after drug administration) and monitor ratings (0–6 hours after drug administration) were used to quantify acute subjective effects. The Intensity subscale of the Hallucinogen Rating Scale (HRS) (Strassman et al., 1994) was used as a global measure of the intensity of the drug experience. The 5-Dimensional Altered States of Consciousness Scale (5D-ASC) (Dittrich, 1998) has 94 items using the visual analog scale format, yielding five primary dimensions: "Oceanic Boundlessness," "Dread of Ego Dissolution," "Visionary Restructuralization," "Auditory Alterations," and "Altered Vigilance." The States of Consciousness Scale is a 100-item questionnaire which has been used extensively to measure states of consciousness in hallucinogen administration experiments (Griffiths et al., 2006; Pahnke, 1963, 1969; Richards et al., 1977; Turek et al., 1974). This scale contains the 43 items of the Pahnke–Richards Mystical Experience Questionnaire (MEQ) (Griffiths et al., 2006). The Addiction Research Center Inventory (ARCI), 49-item version (Martin et al., 1971) was also administered following each drug administration session. In addition, a Monitor Session Rating Form (Griffiths et al., 2006) was completed by both monitors at intervals during the psilocybin sessions to provide ratings of participants' behavior and affect during the session.

Substance use and consequences. The Time-Line Follow-Back (TLFB) (Sobell and Sobell, 1992, 1995) procedure was used to assess drinking behavior at baseline (covering the 12 weeks preceding enrollment) and follow-up visits. Heavy drinking days were defined as days during which participants consumed five or more standard drinks if the participant was male, or four or more standard drinks if the participant was female, a standard drink being defined as 14 g of alcohol. Drinking days were defined as days during which participants consumed any amount (even a sip) of an alcoholic beverage. The Short Inventory of Problems (SIP) (Miller et al., 1995), past 3 month version, was used to measure consequences of alcohol use. Breath Alcohol Concentration (BAC) was measured at each visit, but was used to ensure safety of treatment and validity of assessments rather than as an outcome measure.

Psychological assessments. The Stages of Change Readiness and Treatment Eagerness Scale (SOCRATES 8A) (Miller and

Tonigan, 1996) was used as a measure of motivation. The Alcohol Abstinence Self-Efficacy Scale (AASE) (Diclemente et al., 1994) was used as a measure of self-efficacy to abstain from drinking. The Penn Alcohol Craving Scale (PACS) (Flannery et al., 1999) was used to assess craving. The Profile of Mood States (POMS) (Mcnair et al., 1981) was used as a measure of mood. Additional measures of persisting psychological effects obtained but not discussed in this publication were the Hood Mysticism Scale (Hood et al., 2001), the Persisting Effects Questionnaire (Griffiths et al., 2006), the ASPIRES Spiritual Transcendence Scale (Piedmont, 1999), the Brief Multidimensional Measure of Religiousness/Spirituality (Fetzer Institute, 1999), the NEO Personality Inventory 3 (NEO-PI-3) (Mccrae et al., 2005), and the Schwartz Value Survey (Schwartz, 1992, 2006).

Safety assessment. Vital signs were obtained at each visit and measured frequently during psilocybin sessions: every half hour for the first 2 hours, then hourly for the next 4 hours, with more frequent readings as needed. Adverse events (AEs), when present, were collected on an AE case report form at the end of the psilocybin sessions and at all subsequent visits, including assessment of clinical significance and relatedness to treatment.

Statistical analysis and power

Statistical analyses for this open-label pilot study were primarily descriptive, but two a priori hypotheses were tested. To test for changes in drinking behavior (percent heavy drinking days and percent drinking days), consequences of drinking, and psychological outcomes, scores at follow-up time points were contrasted with baseline and week 4 values using paired *t*-tests, and effect sizes (Cohen's *d*) (Cohen, 1988) were computed with correction for correlation between time points (Morris and Deshon, 2002). The primary drinking outcome was percent heavy drinking days, and the primary contrast was baseline vs. weeks 5–12. With a sample size of $n = 10$, the study had power of 0.803 to detect pre-post changes of effect size $d = 1.0$, with $\alpha = 0.05$ (2-tailed) prior to correction for multiple comparisons. For drinking outcomes, the Benjamini–Hochberg procedure (Benjamani and Hochberg, 1995) was used to control the false discovery rate at the 0.05 level.

Results

Participants

In total 70 individuals were screened for the study, of whom 10 were included in the study (Figure 1). Participants were four women and six men with DSM-IV alcohol dependence. Two participants were Native American/Alaska Native, one was African American, four were Hispanic, and three were white non-Hispanic. Four were single, three were married, and three were divorced. Four were working full-time, five part-time, and one was unemployed. Mean household income was $47,023 (SD $35,262). Participants averaged 15.1 (SD 3.7) years of education (12 years representing graduation from high school), and three were college graduates.

Mean age was 40.1 years (SD 10.3, range 25–56), and mean duration of alcohol dependence was 15.1 years (SD 11.5, range 4–32). Participants had a mean of 5.0 dependence criteria (SD 1.2, range 3–7). Eight out of 10 had evidence of physical dependence (tolerance or withdrawal), but none had alcohol withdrawal symptoms requiring treatment during the trial.

Treatment exposure and follow-up

Figure 1 summarizes participation in treatment and follow-up. Ten participants completed the first psilocybin session. Of the seven participants completing the second psilocybin session, six received psilocybin 0.4 mg/kg and are included in analysis of second session effects. One received psilocybin 0.3 mg/kg due to meeting criteria for "complete mystical experience" in the first session. Nine participants completed all follow-up assessments and are included in outcome analyses. One participant discontinued participation shortly after the first psilocybin session and did not provide usable outcome data. A total of 14 MET sessions were coded for fidelity using the MITI 3.1. Mean (SD) global scores ranged from 4.43 (0.76) to 5.00 (0.00), well above the proficiency benchmark of 4.0.

Acute effects

Figure 2 illustrates physiologic effects and monitor ratings during the first psilocybin session, in which all participants received psilocybin 0.3 mg/kg, and during the second psilocybin session for the six participants who received psilocybin 0.4 mg/kg. Systolic or diastolic blood pressure was modestly but significantly increased from 30 minutes to 180 minutes in one or both conditions. Heart rate (not shown) did not change significantly. Monitor ratings of global drug effect and "distance from ordinary reality" peaked between 120 and 180 minutes, and were significantly elevated at most time points. Differences in these measures between the two doses were not statistically significant (paired *t*-tests, df = 5).

Table 1 shows mean scores on self-report measures of subjective experience obtained 7 hours following administration of psilocybin 0.3 mg/kg in the first session and for the six participants who received psilocybin 0.4 mg/kg in the second session. Intensity of effects varied markedly from patient to patient. On average, acute effects on the MEQ and HRS are numerically lower in magnitude than those seen at comparable doses in normal volunteers (Griffiths et al., 2011). For the six participants who received psilocybin 0.4 mg/kg in the second session, subjective ratings were not significantly different between the two sessions (paired *t*-tests, df = 5), but were strongly correlated between the sessions for most of the scales intended to measure hallucinogen effects.

Clinical outcomes

Percent heavy drinking days decreased during weeks 5–12 relative to baseline (mean difference (SD) = 26.0 (22.4), 95% CI 8.7–43.2, $t(8) = 3.477$, $p = 0.008$), and also decreased relative to weeks 1–4 (during psychosocial treatment but prior to psilocybin) (mean difference (SD) = 18.2 (20.0), 95% CI 2.8–33.5, $t(8) = 2.723$, $p = 0.026$). Percent drinking days also decreased during weeks 5–12 relative to baseline (mean difference (SD) = 27.2 (23.7), 95% CI 9.0–45.4, $t(8) = 3.449$, $p = 0.009$) and relative to weeks 1–4 (mean difference (SD) = 21.9 (21.8), 95% CI 5.1–38.6, $t(8) = 3.010$, $p = 0.017$). Figure 3 illustrates change in

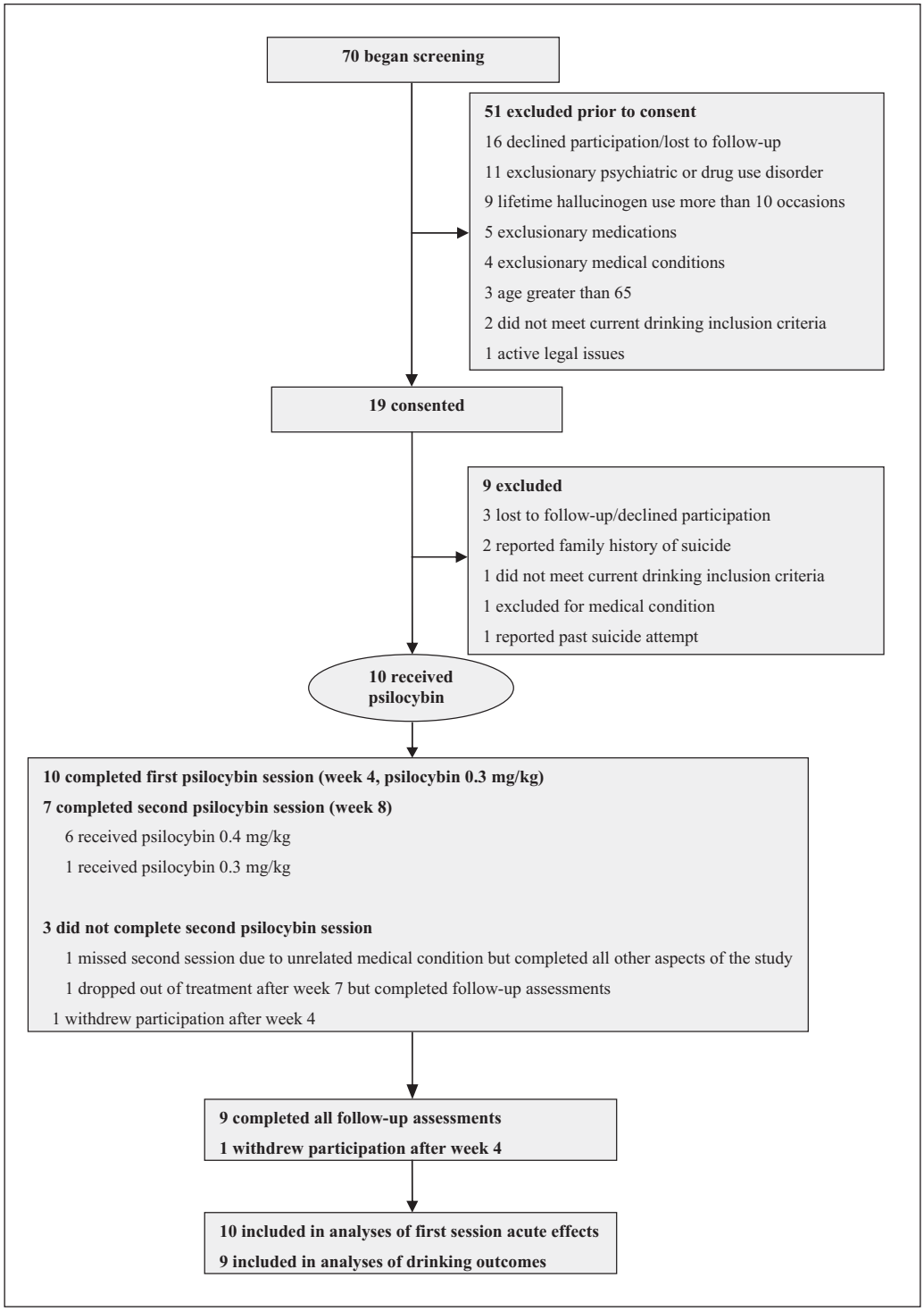

Figure 1. Participant flow.

percent heavy drinking days and percent drinking days over the course of the study. Improvement is not statistically significant during the first 4 weeks of participation, when participants received weekly counseling but had not yet received psilocybin. Following the first psilocybin session, percent heavy drinking days and percent drinking days are significantly lower than baseline at all follow-up points. Further, these measures are significantly decreased relative to weeks 1–4 with the exception of heavy drinking days during weeks 9–12 ($p = 0.059$). Fifteen out of 16 contrasts were significant at the nominal 0.05 level, and all of these remained significant at a false discovery rate of 0.05. Effect sizes are large (greater than 0.8) with one exception, Cohen's *d* ranging from 0.75 to 1.38. Table 2 summarizes additional outcomes for study participants. Significant improvement

relative to baseline and/or week 4 is noted at multiple time points for drinking consequences, craving, self-efficacy, and motivation. Changes in POMS scores were not significant with one exception (increased Vigor at week 24 relative to baseline).

Relationships between acute effects and treatment response

Because the acute effects of psilocybin were quite variable, it was possible to explore the relationships between the intensity of acute effects and changes in drinking behavior. Table 3 shows correlations between three summary measures of the intensity of acute effects in the first psilocybin session and short-term clinical outcomes. Large correlations were observed between measures of acute effect intensity and change in drinking behavior, as well as changes in craving and self-efficacy in some cases. Supplemental Figure 1 displays scatterplots of the individual data points underlying these correlations.

Treatment-related adverse events

Five participants reported mild headaches which resolved within 24 hours following psilocybin administration, consistent with prior reports (Johnson et al., 2012). One participant had nausea with one episode of emesis during one psilocybin session. One participant with irritable bowel syndrome experienced diarrhea during one psilocybin session. One participant reported insomnia on the night following a psilocybin session. No participant required medication or other intervention for blood pressure, anxiety, or other psychiatric symptoms. There was no report of illicit hallucinogen use by any participant during study participation.

Discussion

Overall, the response of our alcohol-dependent participants to psilocybin was qualitatively similar to that which has been reported in other samples (Hasler et al., 2004; Griffiths et al., 2006, 2011; Grob et al., 2011). Medication-related AEs were transient and mild. However, subjective response was highly variable among participants in this study, and numerically weaker on average for some of the measures than that reported in normal volunteers at comparable doses (Griffiths et al., 2011). This is consistent with observations beginning in the 1950s that alcoholics tended to require larger doses of LSD to have a strong effect (Chwelos et al., 1959). Our findings suggest that some alcohol-dependent patients are relatively insensitive to the effects of psilocybin, although larger samples will be necessary to confirm this. The lack of significant differences between the 0.3 mg/kg and 0.4 mg/kg doses is most likely accounted for by the small sample size ($n = 6$) and/or idiosyncratic responses in a small number of participants.

Participants exhibited significant improvement in drinking, with large pre–post effect sizes, as well as significant changes in psychological measures relevant to drinking. Importantly, much of the improvement occurred following the administration of psilocybin, at which time participants had already received 4 weeks of psychosocial treatment and 4–6 hours of assessment. Also, strong correlations were observed between measures of intensity of the acute drug effects and clinical outcomes. Although

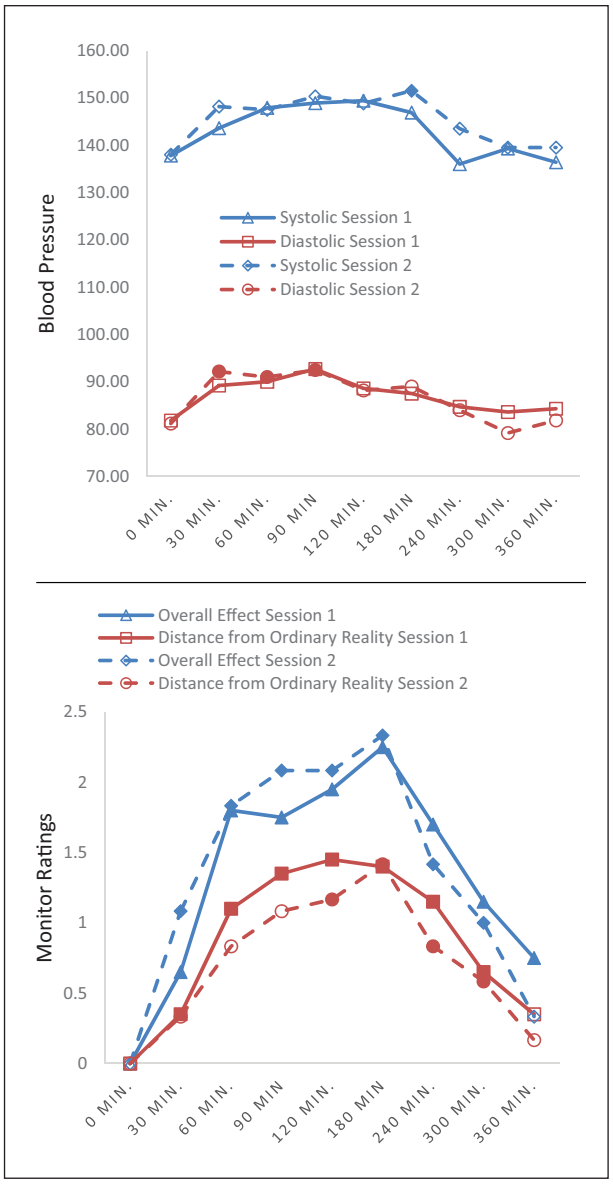

Figure 2. Within-session objective effects. Blood pressure (mm Hg) monitor ratings (0–4 Likert Scale).
Means are shown for 10 participants receiving psilocybin 0.3 mg/kg in the first session (solid lines), and the six participants who received psilocybin 0.4 mg/kg in the second session ($n = 6$, dashed line) during the 6 hours following drug administration. Solid markers indicate significant difference from baseline value.

change in drinking was correlated with the mystical quality of the experience, it was similarly associated with ratings of other acute effects. More work will necessary to determine whether there are particular characteristics of the acute psilocybin experience that are predictive of therapeutic benefit in alcohol use disorder.

While clearly demonstrating feasibility, this study has major, self-evident limitations including small sample size, lack of a control group or blinding, and lack of biological verification of alcohol use. Due to these limitations, it is not possible to separate unequivocally the effects of attention, psychosocial treatment, and time; expectancy effects related to knowledge of receiving psilocybin; and the specific effects of psilocybin. However, the

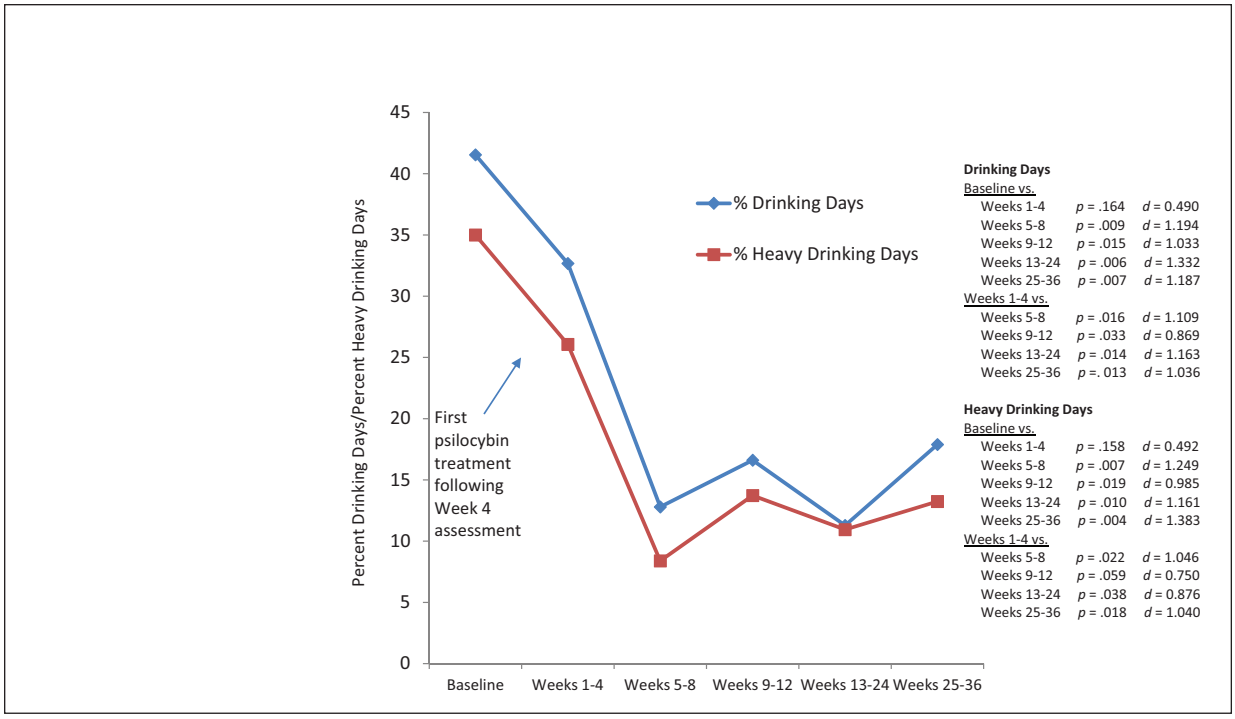

Figure 3. Drinking outcomes and effect sizes.
Means shown are for all available data (n = 10 at baseline, n = 9 at all other time points). p-values are from paired t-tests (df = 8). Cohen's d is shown for the contrast between baseline or weeks 1–4 and each follow-up time point.

Table 1. Acute effects of psilocybin 0.3 mg/kg and 0.4 mg/ kg.

	0.3 mg/kg Session 1 (n = 10)				0.4 mg/kg Session 2 (n = 6)				r	Sig.
	Mean	(SD)	Min.	Max.	Mean	(SD)	Min.	Max.	(n = 6)	
ASC OBN	960.4	(518.8)	91	1798	785.0	(977.3)	79	2107	0.649	0.163
ASC DED	499.6	(515.8)	38	1515	340.1	(445.2)	26	1021	0.808	0.052
ASC VRS	923.5	(396.8)	61	1516	610.2	(543.5)	188	1462	0.670	0.145
ASC AUA	302.5	(380.9)	26	1166	182.0	(288.5)	18	766	0.960	0.002
ASC VIR	394.2	(268.1)	49	819	244.4	(333.0)	36.5	883	0.828	0.042
G-ASC	2383.5	(1347.7)	235	4628	1735.3	(1761.1)	337.5	4590	0.827	0.042
MEQ total	0.473	(0.217)	0.016	0.768	0.387	(0.347)	0.011	0.924	0.843	0.035
HRS intensity	2.43	(1.03)	0	3.5	2.00	(1.14)	0.25	3.25	0.902	0.014
ARCI PCAG	8.00	(3.06)	3	12	5.50	(4.04)	1	12	0.287	0.581
ARCI BG	5.40	(1.58)	3	8	5.83	(2.99)	2	11	0.167	0.752
ARCI A	4.78*	(2.37)	0	8	4.50	(2.88)	2	9	0.198	0.707
ARCI MBG	5.33*	(3.61)	4	12	6.33	(4.55)	2	13	0.388	0.448
ARCI LSD	8.10	(3.21)	1	13	8.17	(2.99)	4	12	0.405	0.425

Shown are scores for all 10 participants in session 1, scores for the six participants who received psilocybin 0.4 mg/kg in the second session, and correlations between scores for the two sessions for these six participants.
*n = 9 due to incomplete questionnaire from one participant.
ASC: 5-Dimensional Altered States of Consciousness Scale; OBN: Oceanic Boundlessness subscale; DED: Dread of Ego Dissolution subscale; VRS: Visionary Restructuralization subscale; AUA: Auditory Alterations subscale; VIR: Vigilance Reduction subscale; G-ASC: summary score (sum of OBN, DED, and VRS); MEQ: Mystical Experience Questionnaire; HRS Intensity: Intensity subscale of the Hallucinogen Rating Scale; ARCI: Addiction Research Center Inventory; PCAG: Phenobarbital, Chlorpromazine, Alcohol Group subscale (sedation); BG: Benzedrine group subscale (stimulant); A: Amphetamine subscale (stimulant); MBG: Morphine-Benzadrine group subscale (euphoria); LSD: LSD subscale (dysphoria). Instruments are described in Methods section.

Table 2. Secondary outcomes.

	Baseline	Week 4	Week 5	Week 8	Week 9	Week 12	Week 24	Week 36
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
SIP								
Physical	4.60 (2.27)					4.89 (3.14)	2.78 (2.95)	2.78 (3.35)
Interpersonal	4.80 (2.57)					4.44 (3.17)	2.56 (3.05)**	2.56 (2.88)**
Intrapersonal	7.30 (1.70)					6.00 (3.12)	3.89 (3.76)*	3.67 (3.74)*
Impulse control	2.90 (1.29)					3.89 (2.47)	2.56 (2.24)	2.56 (3.05)
Responsibility	4.50 (2.37)					4.22 (3.46)	3.67 (3.81)	2.67 (2.87)
PACS	16.00 (5.59)	14.10 (7.17)	11.89 (8.64)	11.56 (5.85)*	10.00 (6.61)**,§	12.11 (8.28)*	13.00 (9.59)	8.11 (9.16)***,§
AASE								
Temptation	38.30 (12.80)	38.10 (18.17)	28.11 (18.86)	32.78 (21.09)	24.56 (16.80)*,§	32.56 (21.67)	26.63 (18.70)*	27.22 (21.86)§
Confidence	40.10 (12.58)	40.30 (16.66)	55.56 (10.88)*,§§	49.00 (11.90)	53.67 (12.76)§	50.00 (13.21)	50.44 (13.09)	54.00 (19.87)§
SOCRATES								
Recognition	31.80 (3.22)	31.10 (5.26)	31.11 (5.33)	31.78 (5.89)	31.89 (5.33)	30.38 (8.02)	28.67 (7.89)	26.78 (9.56)
Ambivalence	15.70 (3.65)	13.90 (5.93)	14.22 (5.31)	14.56 (5.81)	13.11 (6.13)	13.00 (6.48)	12.00* (5.20)	11.56* (4.90)
Taking Steps	32.30 (3.20)	34.00 (5.03)	36.33 (2.65)*	36.33 (2.65)**	37.33 (3.46)**,§	35.78 (3.80)*	36.00 (4.12)*	33.78 (5.36)
POMS								
Tension	7.20 (5.27)	6.22 (3.42)	4.67 (3.54)	5.78 (4.44)	5.89 (4.88)	8.00 6.06	5.78 (5.97)	5.33 (6.04)
Depression	6.50 (5.60)	3.40 (4.45)	4.89 (6.41)	4.44 (3.50)	3.22 (4.38)	6.78 7.45	6.11 (6.11)	5.00 (4.58)
Anger	4.40 (4.09)	2.40 (3.13)	4.67 (4.61)	3.89 (4.62)	2.22 (2.64)	4.50 (6.61)	3.56 (5.48)	4.56 (6.46)
Vigor	5.60 (4.01)	6.50 (3.34)	8.56 (4.61)	8.11 (5.46)	9.00 (5.85)	7.75 4.10	9.56 (4.90)*	7.50 (2.78)
Fatigue	8.70 (5.79)	6.60 (5.78)	6.22 (6.44)	5.44 (4.75)	5.56 (4.28)	7.67 6.28	6.67 (5.96)	6.89 (4.08)
Confusion	6.10 (2.69)	3.90 (1.79)*	4.67 (2.96)	5.33 (3.71)	5.56 (3.43)	5.13 3.36	5.56 (2.19)	4.44 (2.51)

SIP: Short Inventory of Problems; PACS: Penn. Alcohol Craving Scale; AASE: Alcohol Abstinence Self-Efficacy; SOCRATES: Stages of Change Readiness and Treatment Eagerness Scale; POMS: Profile of Mood States.
*Different from baseline, $p < 0.05$; **Different from baseline, $p < 0.01$; ***Different from baseline, $p < 0.001$; §Different from week 4, $p < 0.05$; §§Different from week 4, $p < 0.01$.
$n = 10$ at baseline and 4 weeks, and $n = 9$ at weeks 5–36 with the following exceptions due to missing questionnaire items: $n = 9$ for PACS baseline; $n = 8$ for SOCRATES Recognition week 12, AASE Confidence week 12, AASE Temptation week 24, POMS Anger week 12, POMS Confusion week 12, POMS Vigor week 12, and POMS Vigor week 36.

Table 3. Correlations between acute effects and change in drinking, craving, and self-efficacy (n = 9).

	PDD	PHDD	PACS	AASE
	(wk. 8 – wk. 4)	(wk. 8 – wk. 4)	(wk. 5 – wk. 4)	(wk. 5 – wk. 4)
HRS Intensity	r = –.844	r = –.763	r = –.823	r = .753
(wk. 4)	p = .004	p = .017	p = .006	p = .019
MEQ total	r =–.885	r = –.852	r = –.810	r = .762
(wk. 4)	p = .002	p = .004	p = .008	p = .017
G-ASC	r =–.838	r =–.893	r =–.654	r =-.555
(wk. 4)	p = .005	p = .001	p = .056	p = .121

PDD: Percent Drinking Days; PHDD: Percent Heavy Drinking Days; PACS: Penn Alcohol Craving Scale; [4]AASE = Alcohol Abstinence Self-Efficacy Confidence score; HRS: Hallucinogen Rating Scale Intensity score; MEQ: Mystical Experience Questionnaire; G-ASC: Altered States of Consciousness Scale summary score.

time course of the observed changes and the striking relationship between intensity of response and clinical improvement provide support for the concept that psilocybin may produce lasting benefits in alcohol use disorder when administered under controlled conditions to carefully screened patients, in the context of appropriate psychosocial interventions. Adequately powered randomized trials will be necessary to test this hypothesis rigorously. Neuroimaging studies in alcohol use disorder trial participants would help characterize the persisting effects of psilocybin on brain activity (e.g. resting state functional connectivity, cue response, stress response, response to emotional stimuli, and inhibitory control). Studying the genetics of response to psilocybin may shed light on the variability of response, ultimately aiding in dose selection or identifying patients particularly likely to benefit.

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Harm potential of magic mushroom use: A review

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ABSTRACT

In 2007, the Minister of Health of the Netherlands requested the CAM (Coordination point Assessment and Monitoring new drugs) to assess the overall risk of magic mushrooms. The present paper is an updated redraft of the review, written to support the assessment by CAM experts. It summarizes the literature on physical or psychological dependence, acute and chronic toxicity, risk for public health and criminal aspects related to the consumption of magic mushrooms.

In the Netherlands, the prevalence of magic mushroom use was declining since 2000 (last year prevalence of 6.3% in 2000 to 2.9% in 2005), and further declined after possession and use became illegal in December 2008.

The CAM 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. The combined use of mushrooms and alcohol and the quality of the setting in which magic mushrooms are used deserve, however, attention.

In conclusion, the use of magic mushrooms is relatively safe as only few and relatively mild adverse effects have been reported. The low prevalent but unpredictable provocation of panic attacks and flash-backs remain, however, a point of concern.

1. Introduction

The present paper is a revised version of the technical report used in the assessment of magic mushrooms by the CAM (Coordination point Assessment and Monitoring new drugs). The CAM, an advisory board of experts that provides science-based advises about recreational drugs, was asked by the Dutch Minister of Health to assess the overall risk of psilocine and psilocybine containing mushrooms, i.e. magic mushrooms. The reason to request the assessment was the fatal accident of a French girl who allegedly had consumed magic mushrooms before the accident occurred (cf. case 8 in Section 6.5). Moreover, some other magic mushroom related incidents preceded this fatal accident, and in the same period a report from the Municipal Health Service about magic mushroom related incidents appeared. The expert panel of the CAM, consisting of toxicologists, pharmacists, pharmacologists, policy officers, clinicians, police men, and social scientist/anthropologist, assessed the acute and chronic toxicity, public health, prevalence of use, availability and public order aspects of magic mushrooms. Details on the procedure have been described recently (van Amsterdam et al., 2010). The first author of this review is the secretary of the CAM.

2. Methods

The thematic report of the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), Hallucinogenic mushrooms: an emerging trend case study (EMCDDA, 2010), was taken as a basis for this report. In addition, two literature reviews in Dutch (Bosch et al., 1997; CAM, 2000) were available. This current report was updated with the literature retrieved using searches in the Medline database 2000–2010. Search terms were: 'magic mushrooms', 'hallucinogenic mushrooms', 'LSD', 'psilocybin', 'psilocin', 'suicide', and 'alcohol'. The present review refers to mushrooms that contain psilocybin and/or psilocin. It is explicitly indicated if other mushrooms are described.

3. Magic mushrooms products

The present report reviews psilocine and psilocybine containing mushrooms, i.e. magic mushrooms. Types of magic mushrooms most commonly sold by head or smart shops in the Netherlands are *Psilocybe cubensis* varieties, most notably the *Psilocybe*

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mexicana, none of which are reported to grow wild in Europe. Taken orally, magic mushrooms have a bad taste, and therefore they are sometimes consumed as chocolate bars containing grounded mushrooms.

Magic mushrooms show a large variation in potency; their potency depends on the species or variety that is used, their origin, growing conditions and age. *P. cubensis* and *Psilocybe semilanceata* or *'Psilocybe'*, commonly known as liberty caps, contain 10 mg of psylocybin per gram of dried mushroom weight (1% w/w). Some other species (e.g. *Psilocybe azurenscens and Psilocybe bohemica*) contain slightly more psylocybin. The averaged dose of psilocybin that induces hallucinogenic effects is 4–10 mg (Beck et al., 1998) or 50–300 μg/kg body weight (Hasler et al., 2004), and therefore the minimum amount of mushrooms needed to get the desired recreational effect is about 1 g of dried magic mushrooms or 10 g of fresh magic mushrooms.

The dose 'recommended' for recreational use is reported to be somewhat higher: between 1 and 3.5–5 g of dried mushrooms or 10–50 g for fresh mushrooms (Erowid, 2006). These dose ranges should be interpreted with caution, because it is difficult to estimate the dose of the active or hallucinogenic substance (e.g. psilocybin) into mushrooms (weight or number), as the concentration may vary. Furthermore, in addition to psilocybin and psilocin usually other pharmacologically active substance like indoles, phenylethylamines and baeocystin are present in magic mushrooms. However, as short-term tolerance may develop rapidly to both physical and psychological effect, dosages may have to be increased to obtain the desired effect.

Some mushrooms may contain considerable amounts of phenylethylamine, e.g. up to 150 μg/g wet weight in *P. semilanceata* (Beck et al., 1998). Phenylethylamine is a sympathomimetic amine structurally related to amphetamines, and might be responsible for the cardiovascular effects (tachycardia) and other adverse reactions (nausea and anxiety) of magic mushrooms. Phenylethylamine is not likely to be abused. Its variability in content in mushrooms is much higher than that of psilocybin, which explains why such adverse reactions are relatively infrequent. Interestingly, the psychoactive substances psilocin and psilocybin appear to be more stable in dried mushrooms than in fresh mushrooms. For example, the Dutch Food and Consumer Product Safety Authority (VWA) could only detect traces of both compounds following 4 weeks storage of the fresh magic mushrooms (VWA, 2007).

4. Availability of magic mushrooms

4.1. Availability in the Netherlands

When magic mushrooms were still legal in the Netherlands, the users purchased their mushroom products mainly from smart shops, souvenir shops and via the internet. In a study among a representative sample conducted in 2001, 64% of the users aged 18-years and older purchased their mushroom products in smart shops (Abraham et al., 2002). In 2006, when magic mushroom were still legal in the Netherlands, there some 120–150 smart shops in the Netherlands selling magic mushrooms and other legal psychoactive drugs (Dutch Association of Smart Shop Owners, 2006): about 35 in Amsterdam and a total of about 15 in four other larger towns. Since December 2008 however, the use and possession magic mushrooms has become illegal in the Netherlands, and fresh magic mushrooms are placed on List II in the Dutch Narcotic Law together with cannabis. At the same time, dried magic mushrooms were moved down from List I (hard drugs) to List II. Remarkably, the Dutch legislator did not include the truffle Sclerotia (philosopher stone) in this act of prohibition. Next to the truffle, grow sets of all kinds of mushrooms are still available at smart shops and internet shops. The purchase from internet shops is getting more and more important.

4.2. Availability in Europe

The ESPAD school surveys conducted in 2003 reviewed the accessibility of magic mushrooms to young subjects. It appeared that 4–8% of 15–16 year old school students 'obtain magic mushrooms 'very' or 'fairly' easily, whereas 'easy' access to magic mushrooms was reported by less than 10% of students in Cyprus, Finland, Greece, Hungary, Latvia, Lithuania, Romania and Turkey report and by more than 20% of students in the Czech Republic, Ireland, Italy, Poland and the UK. These levels of access are only estimates of the prevalence of use (probably overestimated). In the Netherlands, despite the lack of legal sanctions to control supply, only 16% of school students in the Netherlands report easy access to magic mushrooms.

Note that following the current trend in many consumer markets, there is a rapid diffusion of new products and brands. For example, the recent prohibition of psilocybin and psilocin containing fungi in the UK appears to have provoked an emerging interest of retailers in legal, types of magic mushroom such as *Amanita muscaria* (fly agaric) (Black Poppy, 2006).

5. Prevalence of use

Overall prevalence estimates for use of magic mushrooms in the EU are considerably lower than those for cannabis. However, life time prevalence estimates appear to equal those for ecstasy among students aged 15–16 years in some countries. Surveys in 12 EU member states indicate that, among young people aged 15–24 years old, life time use of magic mushrooms ranges from less than 1% to 8%. In the UK, almost 340,000 people aged 16–59 ever used magic mushrooms in the last year (2004/5) (Roe, 2005). In the Netherlands, life time use among 15/16 year old students was 5% (Hibell et al., 2003). In a more recent report, but still before magic mushrooms became illegal, Korf and Nabben (2007) report a decreasing trend in use of magic mushrooms. In addition, the authors suggest that the consumption of magic mushrooms is mainly initiated by the user's goal to experiment with drugs in general, and not particularly with magic mushrooms.

In the Netherlands, ever use by young adolescents (14–16 year) decreased from 5% in 1997 to 3% in 2002. The latter figure was confirmed in 2004 (Monshouwer et al., 2004). In older Dutch adolescents, life time prevalence decreased in the same period from 11% to 6%. Similar reductions were found among young visitors of Dutch pubs: last year prevalence of magic mushrooms use decreased from 6.3% in 2000 to 2.9% in 2005. Since the prohibition of magic mushrooms at the end of 2008, the prevalence of use in the Netherlands seems to have largely declined with a last month prevalence in 2009 of 0.1% (Trimbos, 2010).

6. Acute adverse effects

6.1. General side effects

The duration of a 'trip' usually lasts between 2 and 6 h. Mild adverse effects, like sleep problems generally remain present for up to about 12 h. Subjective effects range from intended feelings of relaxation (comparable to those of cannabis), giddiness, uncontrollable laughter, energy, joy, euphoria, visual enhancement (seeing colors brighter), visual disturbances (moving surfaces, waves), to mostly unintended delusions, altered perception of real events, images and faces, or real hallucinations. A survey in the UK in 2004 among 174 magic mushroom users quite high rates of anxiety (32%) and

paranoia (35%) were reported (Riley and Blackman, 2008). In a recent web-based survey on hallucinogenic drugs among 600 subjects showed that the drug effects of magic mushrooms were considered as beneficial with a relatively low harm potential (Carhart-Harris and Nutt, 2010). However, sensory distortions may be coupled with negative effects, like restlessness, impaired coordination, anxiety, impaired judgment of time or distance, sense of unreality or depersonalization. In addition to the differences in psilocybin content consumed, the interpersonal variation in effects is large. A UK clubbing magazine survey conducted in 2005 found that nearly a quarter of those who had used magic mushrooms in the last year had experienced a panic attack (Mixmag, 2005). However, of 150 known cases of intoxication from magic mushrooms in Australia and New Zealand between 1934 and 1989, four subjects showed serious psychological symptoms of which one required hospital care (Allen et al., 1991). Recently, 23 case reports on acute psychiatric symptoms after consumption of magic mushrooms were reviewed by the Nordic Council of Ministers (2009).

6.2. Bad trips

The experience of serious negative effects is often referred to as a 'bad trip'. No exact data are available about the prevalence of a 'bad trip' among regular users. The experience of a bad trip is probably the main reason of users of magic mushroom to visit emergency care facilities. In such cases, the intoxicated individuals are usually severely agitated, confused, extremely anxious, and disoriented with impaired concentration and judgment. Acute psychotic episodes may occur in serious cases, including bizarre and frightening images, severe paranoia and total loss of reality, which may lead to accidents, self-injury or suicide attempts. A bad trip is usually followed by faintness, sadness and depression and paranoid interpretations, which may persist for days, weeks or even months. Some of these symptoms are probably associated with the use of other controlled substances. Occasionally, intermittent and chronic psychotic states due to the use of magic mushrooms are observed. In some individuals, the use of magic mushrooms can exacerbate underlying personality disorders and psychosis-like states. A report on the internet from 2007 (Shroomery, 2007) refers to more severe acute effects by extracts of mushrooms being intravenously injected (Curry and Rose, 1985; Sivyer and Dorrington, 1984). Finally, it is speculated (Satora et al., 2005) that the combined use of magic mushrooms with other psychoactive drugs, including alcohol increases the risk for bad trips.

6.3. Set and setting

The effects (intended as well as unintended, adverse effects) of magic mushrooms depend on "set" and "setting" (Zinberg, 2010). Examples of set factors are individual drug sensitivity, previous experiences, expectations and mental state of the user, whereas setting is the social-cultural environment in which the drug is used. Subjective effects vary greatly within the same person from one episode of use to the next (Jacob and Fehr, 1987; O'Brien, 1996; Pechnick and Ungerleider, 2005). In early clinical research from the 1950s and 1960s, the powerful influences of set and setting on psilocybin effects were neglected. In later studies, subjects were better prepared and interpersonal support was given during the period of drug action. These later studies found fewer adverse psychological effects (e.g. fewer panic reactions and fewer paranoid episodes) and increased reports of positively valued experiences (Leary et al., 1963; Metzner et al., 1965). However, a study by Griffiths et al. (2006) reported that 22% (8 of 36) of the volunteers treated with up to 30 mg psilocybin per 70 kg experienced a period of notable anxiety/dysphoria during the session, some times including transient ideas of reference or paranoia, despite several prior meetings with monitors, with prior contact time ranging from 8 to 24 h. Of the carefully selected volunteers treated with this high dose (30 mg/70 kg), 31% experienced significant fear and 17% had transient ideas of reference/paranoia. A recent meta-analysis of 110 healthy subjects, treated 1–4 times under controlled conditions with 45–315 μg/kg body weight, reported no serious psychological adverse effects (Studerus et al., 2010).

6.4. Acute physical adverse effects

In general, the physiological side effects are not significant and may include dizziness, nausea, weakness, muscle aching, shivering, abdominal pain and dilation of pupils (mydriasis). A UK clubbing magazine survey conducted in 2005 found that over 25 percent of those who had used magic mushrooms in the last year had experienced nausea or vomiting (Mixmag, 2005). Tachycardia is a common finding in patients intoxicated by Psilocybe mushrooms. Mild-to-moderate increase in breathing frequency, heart rate (tachycardia of 10 b.p.m.) and systolic and diastolic blood pressure increase (+25, and +10 mm Hg, respectively) is observed at 0.2 mg/kg psilocybin p.o. (Gouzoulis-Mayfrank et al., 1999), confirming previous data of 8–12 mg/kg p.o. psilocybin (Quetin, 1960). Generally, body temperature remains normal, but pronounced physical symptoms such as severe stomach pain, persistent vomiting, diarrhea etc. have been recorded. The latter physical complaints are not induced by psylocybin itself, but are due to the consumption of mushrooms in general. The tendency for a temporarily increased blood pressure may also be a risk factor for users with cardiovascular conditions, especially untreated hypertension (Hasler et al., 2004).

6.5. Documented fatal incidents

Fatal intoxications due to exposure to magic mushrooms are rare (Gonmori and Yoshioka, 2002; Mccawley et al., 1962) and often due to the combination of magic mushrooms with other drugs, mostly alcohol. The Rand report (Levitt et al., 2006) which refers to the use of magic mushrooms in the UK pointed out that that "National Statistics of the UK show that for death in which drug poisoning (listed on the certificate) was the underlying cause of death, between 1993 and 2000 there was one death from magic mushrooms and 5737 from heroin". Note that these figures from the UK National Statistics do not include deaths in which the misuse of drugs was a contributory factor rather than the cause of the death, and represent therefore an underestimate. The report further indicates that the lethal dose of magic mushrooms for humans is very low. As the oral LD_{50} value of psylocybin in the rat is 280 mg/kg, 17 kg of fresh mushrooms must be consumed to reach this rate in an adult human subject. Indeed, only two fatal cases (Gerault and Picart, 1996; Bück 1961) have been described in literature which are due to overdosing with magic mushrooms (no concomitant use of other drugs). Normally, people do not die from a magic mushroom overdose, because they are not very toxic en the potential victim will spontaneously vomit keeping the final dose low.

Additional fatal cases reported in open and 'grey' literature are described below.

1. A 6-year old child developed hyperthermia and status epilepticus following ingestion of *Psilocybe baeocystis* (Mccawley et al., 1962).
2. A 31 year old English man died after leaping from a tower block window after consuming 'Hawaiian' psilocybin containing mushrooms in combination with alcohol (Manchester Evening News, 28.05.2005). A coroner confirmed the contributory role of magic mushrooms together with alcohol: the amount of alcohol consumed was two and a half times the drink drive limit.

3. A 33 year old Irish man died after falling from the fourth floor of a building after consuming magic mushrooms and alcohol (Irish Independent, 02.03.2006).
4. A young French girl died after trying 'to fly' from the window of her room on the second floor after taking magic mushrooms (Asselborn et al., 1999). The autopsy revealed a traumatic cause of death, and post-mortem toxicological analysis indicated consumption of psilocybin and cannabis. Psilocybin concentrations were 0.06 mg/l for venous blood and 0.22 mg/l for heart blood. Moreover, her blood contained three cannabinoids (THC: 30 μg/l; 11-OH-THC: 8 μg/l and THC-COOH: 90 μg/l).
5. A 27-year-old Frenchman was found dead in an irrigation canal in winter time. The toxicological examination confirmed the ingestion of a large amount of mushrooms (*Psilocybe subcubensis*). It was concluded that he died of cold temperature in winter time (Gonmori and Yoshioka, 2002).
6. In 2004 one suicide was reported in the Czech Republic, in which the presence of magic mushrooms was confirmed by autopsy (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).
7. An 18-year old male on Hawaii allegedly died after consumption of ten magic mushrooms. Later it was shown that the victim died of an overdose of heroin; no psilocybin was detected in the stomach (Allen, 1988).
8. A young French girl who had allegedly used magic mushrooms jumped from a building in Amsterdam (CAM, 2007). Blood tests were, however, not performed to ascertain use of magic mushrooms.
9. Two young foreign male tourists died after they jumped out of the window of an Amsterdam hotel after the consumption of magic mushrooms (Buster and van Brussel, 2007).
10. A 18-year old Dutch male died after he jumped out of the window. According to the police he had used magic mushrooms (De Telegraaf, 2008).
11. A 20-year old Dutch male died after he became sick following the use of magic mushrooms, ecstacy and alcohol (De Gelderlander, 2008).

6.6. Interaction of magic mushrooms with other drugs

Both psilocine and psilocybine are dimethyltriptamines (DMT's), which are rapidly metabolized (inactivated) by the enzyme MAO (mono amine oxidase, which catalyses the oxidative deamination of biogenic amines). As such, MAO-inhibitors inhibit the metabolization of DMT's. Acetaldehyde, the primary metabolite of ethanol, reacts in vivo with endogenous biogenic amines thereby producing the MAO-inhibitors tetrahydroisoquinolines (TIQs) and β-carbolines (tryptolines). Thus, it is speculated that alcohol may enhance the trip (and adverse effects!) induced by magic mushrooms. Though chocolate also contains MAO-inhibitors, the amount of MAO-inhibitors in regular chocolate is clinically not relevant. Finally, tobacco use is associated with lowered levels of MAO in the brain and peripheral organs (prolonged effects; recovery following smoking cessation) (Fowler et al., 1996; van Amsterdam et al., 2006). Tobacco smokers may therefore experience more pronounced desired and adverse effects of magic mushrooms as compared to non-smokers.

7. Chronic toxicity

7.1. Flashbacks

Flashbacks are spontaneous recurrences of a previous psilocybin experience (perceptual alterations, pseudo-hallucinations) without renewed intake of the drug. Flashbacks may occur long (days, weeks or even years) after having used magic mushrooms (Benjamin, 1979). A critical review (Halpern and Pope, 2003) of 20 quantitative studies about the so-called Hallucinogen Persisting Perception Disorder (HPPD; Flashbacks) concluded that the current knowledge is very limited. HPPD appears to be an existing, but uncommon disorder, sometimes persisting for months or years after hallucinogen use. HPPD is reported mostly after LSD use, but less commonly with the use of magic mushrooms or LSD administered in research or treatment settings (Halpern and Pope, 2003). Indeed, in the study of Carhart-Harris and Nutt (2010), based on 600 forms submitted via the web, 38 out of the 174 subjects who used all drugs reported symptoms of hallucinogen persisting perceptual disorder (flashbacks). When those 38 subjects were asked which drug was most responsible for the flashback, 55% answered LSD and 22% psilocybin. In most reports on flashbacks the subject was a poly-drug user or a psychiatric patient at the time of use.

7.2. Psychosis and other psychiatric diseases

In a series of studies about the acute subjective, psychological, and perceptual effects of psilocybin it was shown that psilocybin induces a psychotic state that mimics certain aspects of acute and incipient stages of schizophrenia (Carter et al., 2005; Hasler et al., 2004; Vollenweider et al., 1998; Gouzoulis-Mayfrank et al., 1998; Vollenweider et al., 1998; Vollenweider and Geyer, 2001). Though these reports do not establish a causal relation between psilocybin and psychiatric disease, the possible role of hallucinogens in precipitating or exacerbating enduring psychosis, other psychiatric conditions, and long-lasting visual perceptual disturbances should be assessed more closely (Abraham et al., 1996; Halpern and Pope, 1999). A similar association has been claimed with respect to the use of cannabis, which is also assumed to exacerbate psychosis in vulnerable subjects (van Amsterdam and van de Brink, 2004). It is, therefore, advocated, that psychiatric patients and genetically susceptible subjects i.e. those with a family history of psychiatric disease should fully abstain from the use of any recreational drug. In schizophrenic patients the consumption of magic mushrooms may induce an acute psychotic state that necessitates hospitalization (Nielen et al., 2004).

8. Physical and psychological dependence

The authors could not find any evidence that magic mushrooms can lead to physical or psychological dependence. Tolerance to the psychedelic effects of psilocybin develops rapidly, but withdrawal symptoms and psychological dependency do not occur (Abramson and Rolo, 1965; Isbell et al., 1961) or are very rare compared to all other (illegal) drugs (Anthony et al., 1994; Stone et al., 2006; Stone et al., 2007).

9. Public health effects

9.1. Availability of adequate user information

Many young tourists visit the Netherlands (especially Amsterdam) to use magic mushrooms which until recently were easy available in legal smart shops. Most incidents with magic mushroom occur in foreign tourists and not in Dutch users. Therefore, retailers from the smart shops provide warnings in English about the use of magic mushrooms. These leaflets warned specific groups to refrain from using magic mushrooms. The groups at risk are: persons under the age of 18, pregnant women, patients who use pharmaceutical drugs or suffer from a mental illness, and people who drive or operate machines. They also warned not to use magic mushroom in combination with alcohol, and to start mushrooms

consumption by taking small portions, because the aimed effect is delayed due to slow uptake into the blood using this route of dosing. Occasionally, the number of a UK Drug Help line is displayed on the label. However, the quality of the information provided by those selling the product varies (CAM, 2000). Most leaflets provide some information about the maximum shelf life, the nature of possible side-effects and the amount of active substances (psilocybin and psilocin). In 2006, most of the online shops warned against the use magic mushrooms when taking medication and/or in combination with alcohol or other drugs such as stimulants, but only two thirds warn against the use of magic mushrooms when the user suffers from depression or psychosis. Many o these internet sites of the online shops provide information on the intended use, but only few provide information on the safe use and the possible adverse effects of magic mushrooms. In general, the information from the retailers is biased towards the positive effects.

9.2. Emergencies related to the use of magic mushrooms

In Europe, the reported number of people seeking medical assistance for magic mushrooms intoxication is very low. In Toxicological Information Centers of the Slovak Republic the number of intoxications with all natural drugs increased 5-fold between 2001 and 2002 and poisonings due to mushrooms (not specified) was 4.3% of all poisonings (Kresanek et al., 2005). Mushroom poisonings are also common in Poland, especially in summer and autumn and are associated with traditional wild-mushroom picking and cookery. However, very few (2–4 psilocybe intoxications are reported annually by the Polish toxicological center (Satora et al., 2005). A data summary from the Swedish Poison Information Centre collected over 15 years in the period 1980–1995 reported only 25 cases of patients with Psilocybe mushroom intoxication (Beck et al., 1998). Of these patients, 10 showed anxiety; 4 agitation; 3 flushing; 3 nausea/vomiting; and 2 flashbacks. A more recent report from this source indicates that in the last 5 years the number of cases increased considerably to around 30–40 calls annually, though this is still relatively low. The Dutch National Poisoning Information Center (NVIC) reported 60 requests for information about magic mushroom poisoning per year, and this number was stable over the years 2001–2006 (NFI, 2007). Since the prohibition of magic mushrooms in the Netherlands in December 2008, the number of such information requests decreased (in 2007, 2008 and 2009 the number was 67, 57, and 14, respectively).

In 2005, the Amsterdam Municipal Health Service registered 2837 calls for ambulance service assistance related to recreational drug use (Buster and van Brussel, 2007). Alcohol intoxication was the most frequent reason of an emergency call (2056 times; 72.5%), whereas for magic mushroom use it was 70 times (2.5%). Most of the calls referred to ambulance services given to tourists: 92% of magic mushroom 'victims' were foreigners. In contrast to incidents related to cocaine, heroin and ecstasy, magic mushroom related incidents were relatively harmless: treatment in an intensive care unit was needed for 11–20% of the group who had used cocaine, heroin or ecstasy, and for 1.5% of those who had used magic mushrooms. More importantly, it is highly probable that the combined use of magic mushrooms with either alcohol or cannabis was the major cause of the incidents (no exact data available). Finally, magic mushroom incidents occurred mainly (95%) in public places (street, bars, hotels), which is considerably higher as compared to incidents related to the use of the cocaine, heroin, XTC and alcohol (60–70%). Since the prohibition of magic mushrooms in December 2008, the number of calls for ambulance assistance related to the use of magic mushrooms has declined from 117 in 2008 to 53 in 2009.

In the period 2004–2006, the Dutch National Forensic Institute (NFI) investigated the presence of psilocybin in urine of subjects deceased under suspicious circumstances, including unnatural death, use of drugs in traffic, and criminal cases where subjects were doped. Psilocybin was probably involved (detected in urine) in only 4 of the 4636 cases investigated (NFI, 2007).

10. Public order and safety

Theoretically, a magic mushroom user could behave recklessly during a mushroom trip, and panic attacks during a 'bad trip' could evoke aggressive behavior. Forensic physicians in Amsterdam have registered 30–36 lock-ins at police stations related to magic mushroom intoxications per year. Main reasons to lock the subjects in were public nuisance (71%) and violation of traffic rules (27%). For comparison: the number lock-ins for alcohol was 1846 (Buster and van Brussel, 2007). It should be noted that psilocybin (100–250 μg/kg p.o.) affects the subjective perception of time, synchronization and tapping tempo, working memory and subjective changes in conscious state (Hasler et al., 2004), which largely impairs car driving and handling of machines (Wittmann et al., 2007).

11. Criminal involvement

The Dutch National Criminal Intelligence Service found no evidence of public nuisance as a result of sale or use of magic mushrooms. The 2007-briefing of the Dutch National Police Forces (KLPD, 2007) reports no criminal acts related to magic mushrooms, no relations between magic mushroom growers and criminals, no offenders of law related to magic mushrooms, except for two offences in one shop for selling dried magic mushrooms (the shop is temporarily closed). Occasionally, the police receives postal mailings containing illegal dried magic mushrooms with destinations abroad (which were undeliverable). The border police at the Belgium border regularly observed the export of dried mushrooms to France, Belgium and Luxembourg, which are confiscated. The customs at the national airport (Amsterdam Schiphol) occasionally confiscated small amounts (some kilograms) of magic mushrooms. In 2006–2007, the German customs found and confiscated one large mailing of 27 kg magic mushrooms.

12. Conclusion

It is concluded, that the use of magic mushrooms rarely (if ever) leads to physical or psychological dependence, that acute and chronic adverse effects are relatively infrequent and generally mild, that public health and public order effects are very limited and that criminality related to the use, production and trafficking of magic mushrooms is almost non-existent. However, attention should be paid to the infrequent occurrence of flashbacks and accidents. More specifically, in the absence of proper surveillance of the user the panic attacks evoked by magic mushroom use may lead to severe and sometimes fatal accidents.

The list mentioned in Section 6.5 is partly based on newspaper articles and will probably not be complete. On the other hand, fatal accidents were sometimes (e.g. case 8–11) attributed to the use of magic mushrooms although the evidence was not available (no autopsy or blood test report). Furthermore, the reported fatal accidents and suicides will not always appear as mushroom related deaths in the official statistics. Still, the infrequent but severe adverse effects are often associated with overdosing and the combined use with other drugs, including alcohol. When using magic mushrooms, many, if not all, accidents can be prevented by a supporting setting, such as surveillance by a 'sober' person. An attractive option is to make psilocybin available for use only on premises, e.g. in specially designed environments for this purpose.

The results of this review have been used in a recent study to rank the relative harm of magic mushrooms compared to a selection of 19 illicit drugs, including heroin, cocaine, ecstasy and cannabis. Based on the rating of 19 experts for 19 recreational drugs for dependence potential, acute and chronic adverse health effects, prevalence, social harm and criminality, magic mushrooms were ranked as the illicit drug with the lowest harm (van Amsterdam et al., 2010). Similar low harm ratings for magic mushrooms were reported by two expert groups in the UK (Nutt et al., 2010, 2007; van Amsterdam et al., 2010).

Based mainly on the content of the expert CAM report, the overall risk potential of magic mushrooms use was judged to be very low and the CAM advised the Minister of Health to maintain the legal status of magic mushrooms. However, because the generation of panic attacks by magic mushrooms is unpredictable, and the panic attacks have resulted in the (fatal) accidents observed among some tourists, the Dutch Minister of Health prohibited the possession, use, production and trafficking in December 2008 (Expatica Communications B.V., 2008). Like cannabis, magic mushrooms are now classified as a 'List II drug' in the Dutch Narcotic Law. This decision was taken despite the advice of the CAM expert panel.

Conflict of interest

The authors declare that there are no conflicts of interest.

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3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial

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Summary

Background Post-traumatic stress disorder (PTSD) is prevalent in military personnel and first responders, many of whom do not respond to currently available treatments. This study aimed to assess the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treating chronic PTSD in this population.

Methods We did a randomised, double-blind, dose-response, phase 2 trial at an outpatient psychiatric clinic in the USA. We included service personnel who were 18 years or older, with chronic PTSD duration of 6 months or more, and who had a Clinician-Administered PTSD Scale (CAPS-IV) total score of 50 or greater. Using a web-based randomisation system, we randomly assigned participants (1:1:2) to three different dose groups of MDMA plus psychotherapy: 30 mg (active control), 75 mg, or 125 mg. We masked investigators, independent outcome raters, and participants until after the primary endpoint. MDMA was administered orally in two 8-h sessions with concomitant manualised psychotherapy. The primary outcome was mean change in CAPS-IV total score from baseline to 1 month after the second experimental session. Participants in the 30 mg and 75 mg groups subsequently underwent three 100–125 mg MDMA-assisted psychotherapy sessions in an open-label crossover, and all participants were assessed 12 months after the last MDMA session. Safety was monitored through adverse events, spontaneously reported expected reactions, vital signs, and suicidal ideation and behaviour. This study is registered with ClinicalTrials.gov, number NCT01211405.

Findings Between Nov 10, 2010, and Jan 29, 2015, 26 veterans and first responders met eligibility criteria and were randomly assigned to receive 30 mg (n=7), 75 mg (n=7), or 125 mg (n=12) of MDMA plus psychotherapy. At the primary endpoint, the 75 mg and 125 mg groups had significantly greater decreases in PTSD symptom severity (mean change CAPS-IV total scores of –58·3 [SD 9·8] and –44·3 [28·7]; p=0·001) than the 30 mg group (–11·4 [12·7]). Compared with the 30 mg group, Cohen's *d* effect sizes were large: 2·8 (95% CI 1·19–4·39) for the 75 mg group and 1·1 (0·04–2·08) for the 125 mg group. In the open-label crossover with full-dose MDMA (100–125 mg), PTSD symptom severity significantly decreased in the group that had previously received 30 mg (p=0·01), whereas no further significant decreases were observed in the group that previously achieved a large response after 75 mg doses in the blinded segment (p=0·81). PTSD symptoms were significantly reduced at the 12-month follow-up compared with baseline after all groups had full-dose MDMA (mean CAPS-IV total score of 38·8 [SD 28·1] *vs* 87·1 [16·1]; p<0·0001). 85 adverse events were reported by 20 participants. Of these adverse events, four (5%) were serious: three were deemed unrelated and one possibly related to study drug treatment.

Interpretation Active doses (75 mg and 125 mg) of MDMA with adjunctive psychotherapy in a controlled setting were effective and well tolerated in reducing PTSD symptoms in veterans and first responders.

Funding Multidisciplinary Association for Psychedelic Studies.

Introduction

Post-traumatic stress disorder (PTSD) is a major public health problem, particularly among military veterans. Prevalence of PTSD in military personnel and veterans (17·1%)[1] and first responders (10–32%)[2] is much higher than the lifetime occurrence in the general population (8%). In addition to the severe psychological burden, chronic PTSD is associated with increased medical morbidity, occupational and relationship problems, decreased quality of life,[3] overall decreased life satisfaction and happiness, and increased risk of suicide.[4]

Treatment options for PTSD include pharmacotherapy and psychotherapies. The two medications approved by the US Food and Drug Administration (FDA) for PTSD, sertraline and paroxetine, reduce symptom severity with limited effectiveness,[5] especially in veterans. Off-label prescription of drugs, including antidepressants,

Research in context

Evidence before this study

Before development of this study's protocol, we searched PubMed, ClinicalTrials.gov, and books containing extensive bibliographies of 3,4-methylenedioxymethamphetamine (MDMA) research for all articles and listings containing the terms "MDMA" or "ecstasy", including non-clinical studies, clinical trials, and case reports of varying quality published from Jan 1, 1978, to Dec 17, 2009. We considered all these articles published in English only, except for case reports. In 2001, the first comprehensive review was presented in our MDMA Investigator's Brochure; 1044 MDMA-related papers were included. Early reports published in the mid-1980s described the use of MDMA as a psychotherapeutic adjunct, including use in psychotherapy for post-traumatic stress disorder (PTSD). These accounts, an early uncontrolled study, and an incomplete dose-response study that provided safety data led to the design and implementation of two randomised, double-blind studies of MDMA-assisted psychotherapy in people with chronic PTSD, one using inactive placebo and the other comparing an active low dose of MDMA. The studies followed a manualised form of psychotherapy similar but not identical to psychotherapy using classic psychedelics. The current study design was informed by confirmation that no other research of MDMA-assisted psychotherapy had been published, and by the design and preliminary results of two pilot studies that were ongoing at the time of development of this study. When completed, one pilot study reported a significant reduction in PTSD symptoms in MDMA versus inactive placebo that lasted beyond 12 months after study completion. The second pilot study had a similar effect size as the first study, but did not detect a significant difference in the Clinician-Administered PTSD Scale (CAPS-IV) scores 2 months after treatment (p=0·066); however, it did show significant symptom reduction compared with baseline 1 year after treatment with active-dose MDMA.

Added value of this study

In this first dose-response study of MDMA-assisted psychotherapy to compare three doses of MDMA, in a population of first responders and veterans with PTSD, we showed that active doses of MDMA had a significant improvement compared with the control dose in the primary measure of PTSD symptom severity, as well as in some of the secondary measures of depression symptoms and sleep quality, confirming and extending findings of the first studies..

Implications of all the available evidence

This study is among the six phase 2 trials that led to the US Food and Drug Administration designation of MDMA-assisted psychotherapy for PTSD as a breakthrough therapy. Together these phase 2 trials support the drug development programme of the Multidisciplinary Association for Psychedelic Studies aimed at making MDMA-assisted psychotherapy a prescription treatment delivered in specialised clinics. Pending the results of multicentre phase 3 clinical trials, this well tolerated and efficacious treatment might prove to be an important addition to the available treatments for PTSD, and might also have implications for future exploration of other pharmacological agents that could act as adjuncts or catalysts to psychotherapy.

antipsychotics, mood stabilisers, and benzodiazepines, is common, although risks and benefits for PTSD have not been established in randomised controlled trials. Trauma-focused psychotherapies are more effective than pharmacotherapy.[6] A meta-analysis of trials for military-related PTSD found that both cognitive processing therapy and prolonged exposure therapy had large effect sizes with 49–70% of participants attaining clinically meaningful symptom improvement; however, 60–72% of veterans receiving either of these therapies retained their PTSD diagnosis.[7] High dropout (27–40%) occurs with trauma-focused psychotherapies, partially due to adverse outcomes, such as worsening symptoms, admission to hospital, or disengagement from treatments.[8,9] Relatively few randomised clinical trials of military-related PTSD have been done.

Development of new treatments should address the common reasons for treatment avoidance, failure, and dropout. One approach to developing more effective psychotherapy is to administer a drug during psychotherapy sessions intended to catalyse the psychotherapeutic process.[5,10] 3,4-methylenedioxymethamphetamine (MDMA) has shown promise as a psychotherapeutic adjunct.[11] Two published clinical trials of MDMA-assisted psychotherapy showed large effect sizes (1·24 and 1·05) with low dropout (8·7% and 14·3%)[12,13] and durable improvements (average 45 months in 74% of one cohort).[14] Most participants had crime-related PTSD, such as sexual abuse, assault, and rape. Therefore, we aimed to assess the efficacy and safety of MDMA-assisted psychotherapy in military veterans, firefighters, and police officers with PTSD resulting from their service.

Methods

Study design and participants

We did a randomised, double-blind, dose-response, phase 2 trial at an outpatient psychiatric clinic in Charleston, SC, USA. The protocol for this study was approved by Western-Copernicus Group institutional review board. The protocol provides full details of the study design.

For the **study protocol** see https://s3-us-west-1.amazonaws.com/mapscontent/pdfs/MP-8_FINAL_Protocol_Amendment+5_16Aug13_REDACTED.pdf

We recruited participants through referrals by mental health professionals and internet advertisements or word of mouth. We included participants of either sex who were veterans, firefighters, or police officers with chronic PTSD resulting from traumatic experience during their service. Additionally, we included only participants who were

18 years or older, with PTSD duration of 6 months or more, and who had a Clinician-Administered PTSD Scale (CAPS-IV)[15] total score of 50 or more. Inclusion criteria required failure to respond to or inability to tolerate previous pharmacotherapy or psychotherapy. Participants were required to taper and abstain from psychotropic medications during study participation except for sedative hypnotics or anxiolytics used as needed between MDMA sessions. Exclusion criteria included major medical conditions except controlled hypertension or adequately treated hypothyroidism, and pregnant or lactating women or women not using effective contraception. Permitted comorbid disorders were anxiety disorders, affective disorders except bipolar disorder type 1, substance abuse or dependence in remission for 60 days or more, and eating disorders without active purging. We also had an additional exclusion criterion that cannot be revealed publicly until a future phase 3 trial is complete.

Participants who gave written informed consent were assessed by an independent rater for psychiatric screening using the CAPS-IV and Structured Clinical Interview for DSM-IV Axis I Disorders,[16] and by a physician for assessment of non-psychiatric medical criteria.

Randomisation and masking

We randomly assigned participants using a web-based randomisation system that used unique container numbers instituted by individuals monitoring the randomisation process who did not communicate with site staff, those monitoring the study, or data and statistical analysts. Approximately 24 h before the first experimental MDMA session, participants were randomly assigned (1:1:2) to three different dose groups of MDMA plus psychotherapy. We masked investigators, independent outcome raters, and participants until after the primary endpoint. After the primary endpoint, the blind was broken and the study entered the crossover design, which was open-label. MDMA was manufactured by David Nichols (Purdue University, West Lafayette, IN, USA). A pharmacist compounded the drug into gelatin capsules with lactose to ensure all blinded capsules had similar appearance and weight.

See Online for appendix

Procedures

Depending on the dose groups, MDMA was administered orally at 30 mg (active control), 75 mg, or 125 mg in two blinded experimental sessions spaced 3–5 weeks apart (initial dose followed 1·5–2 h later by an optional supplemental dose of half the initial dose). Figure 1 depicts the flow of participants through the study.

The first MDMA session was preceded by three 90-min psychotherapy sessions to establish a therapeutic alliance and prepare participants for the MDMA experience. MDMA was administered at monthly intervals during 8-h experimental sessions of manualised psychotherapy with a male or female co-therapy team. The relatively non-directive or client-directed psychotherapy used during MDMA-assisted sessions, and the approaches to preparation and follow-up sessions, are described in the treatment manual.[17] Experimental sessions were followed by an overnight stay onsite, 7 days of telephone contact, and three 90-min psychotherapy sessions aimed at integrating the experience. Overall, a course of treatment included 18 h of non-drug psychotherapy and 16–24 h (2–3 sessions) of MDMA-assisted psychotherapy. Outcome measures were administered by masked independent raters at baseline and 1 month after the second experimental session (primary endpoint), just before the blind was broken.

Subsequently, participants randomly assigned to receive 125 mg of MDMA had one open-label session (within 3–5 weeks of the previous blinded MDMA session) with associated integrative visits and a 2-month follow-up with outcomes assessed (end of stage 1). Participants randomly assigned to receive 30 mg or 75 mg of MDMA crossed over to have one 90-min preparatory session (within 5 months of the primary endpoint), then three open-label sessions spaced a month apart with flexible dosing of MDMA (100–125 mg) followed by the integrative visits and outcome assessments (secondary endpoint, end of stage 2) at corresponding intervals to the blinded segment.

Data were collected during the active treatment period from baseline to 2 months after the final MDMA session, and participants in all three groups were assessed 12 months after the last full dose. A choice between 100 mg and 125 mg (according to the participant's preference and investigators' judgment) was added in the open-label crossover as part of a protocol amendment (appendix) to gain pilot data about this dose without affecting the blinded stage of the study.

Outcomes

The primary outcome was mean change in the CAPS-IV total score from baseline to 1 month after the second experimental session. CAPS-IV is a semi-structured interview done by an independent rater that identifies and assesses PTSD through diagnostic and symptom severity scores.

Secondary outcomes included the following measures: depression symptoms, measured with the self-reported Beck Depression Inventory-II (BDI-II);[18] self-reported sleep quality, assessed by the Pittsburgh Sleep Quality Index (PSQI);[19] perceived growth following trauma, assessed with the Post-Traumatic Growth Inventory (PTGI);[20] personality factors, assessed via the Neuroticism-Extroversion-Openness-Personality Inventory-Revised (NEO-PI-R);[21] symptoms of dissociation, assessed in a subset of participants with the self-reported Dissociative Experiences Scale II (DES-II);[22] and general psychological function, scored by independent raters using the single-item Global Assessment of Functioning (GAF).[23]

Safety was monitored through adverse events, spontaneously reported expected reactions, vital signs,

and suicidal ideation and behaviour. Adverse events requiring medical intervention were recorded until 2 months following the last experimental session. Events requiring changes in psychiatric medication were recorded throughout the study. Expected reactions were recorded during experimental sessions and 7 days after the sessions. Blood pressure and heart rate were measured via an automated sphygmomanometer (5200 series, Welch Allyn, Skaneateles Falls, NY, USA) every 15 min for the first 4 h, then every 30 min until the session ended. Body temperature was measured at 60–90 min intervals via a tympanic thermometer (Thermo Scan, Braun, Kronberg, Germany). The clinician-administered Columbia-Suicide Severity Rating Scale (C-SSRS),[24] a structured interview addressing presence and intensity of suicidal ideation and behaviour, was used at all visits and twice during the 7 days of telephone contact.

Statistical analysis

This trial was a pilot dose-response study; therefore, it was not powered to detect statistical significance. The study design and sample size were informed by two previous phase 2 pilot studies.[12–14] Efficacy analyses were done on the intention-to-treat population, which included all participants who were randomly allocated to the dose groups of MDMA with at least one dose exposure. The primary outcome measure was analysed by ANOVA at an α level of 0·05. Preplanned *t* tests were used to compare each MDMA dose group. Changes in the secondary measure scores were analysed in the same manner. Effect sizes were computed with Cohen's *d* independent-groups pretest–post-test design. Open-label crossover data were analysed by within-subjects *t* tests, comparing scores at primary endpoint to stage two secondary endpoint. Scores at 12-month follow-up were compared with baseline by within-subjects *t* tests. Exploratory analyses of effects after two versus three sessions were also done with within-subjects *t* tests. Peak vital signs from MDMA sessions were analysed with ANOVA, then *t* tests for pairwise comparisons. We did the analyses using SPSS (version 20). This trial is registered with ClinicalTrials.gov, number NCT01211405.

Role of the funding source

MAPS Public Benefit Corporation (MPBC), a wholly owned subsidiary of the Multidisciplinary Association for Psychedelic Studies (MAPS), was the trial organiser. Both the funder and MPBC assisted with study design; monitoring of study data; analysis, management, and interpretation of data; preparation, review, and approval of manuscript; and decision to submit the manuscript for publication. The funder had no role in data collection or study conduct. The first author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

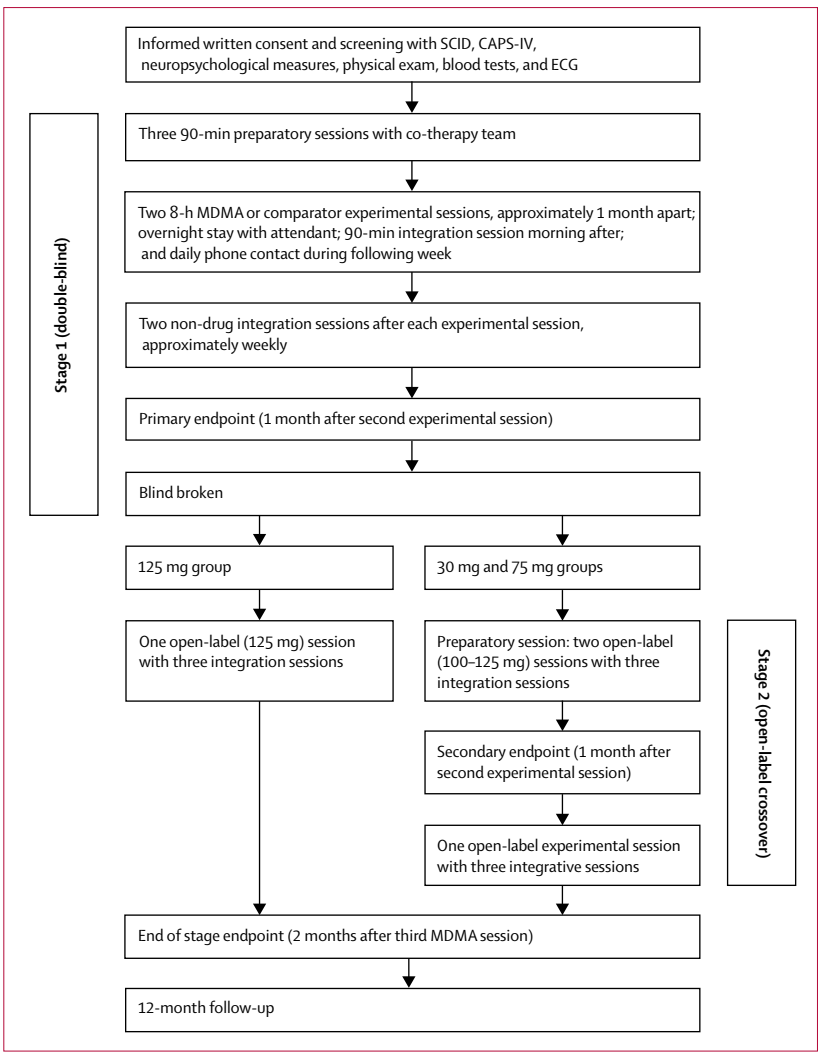


Figure 1: **Study design**
SCID=Structured Clinical Interview for DSM-IV Axis I Disorders. CAPS-IV=Clinician Administered PTSD Scale. PTSD=post-traumatic stress disorder. ECG=electrocardiogram. MDMA=3,4-methylenedioxymethamphetamine.

Results

Between Nov 10, 2010, and Jan 29, 2015, 26 service personnel met eligibility criteria and were enrolled into this study: four participants enrolled through referrals by mental health professionals and 22 through internet advertisements or word of mouth. These 26 participants were randomly assigned to receive 30 mg (n=7), 75 mg (n=7), or 125 mg (n=12) of MDMA plus psychotherapy (figure 2). Table 1 shows the baseline characteristics and demographics of these veterans (n=22), firefighters (n=3), and police officer (n=1). Participants had moderate-to-severe PTSD, with a mean baseline CAPS-IV total score of 87·1 (SD 16·13). Six (23%) of 26 participants had previously taken ecstasy 2–5 times before study enrolment. 24 (92%) participants completed treatments through the 1-month follow-up, and two (8%) completed the baseline assessment (one experimental session,

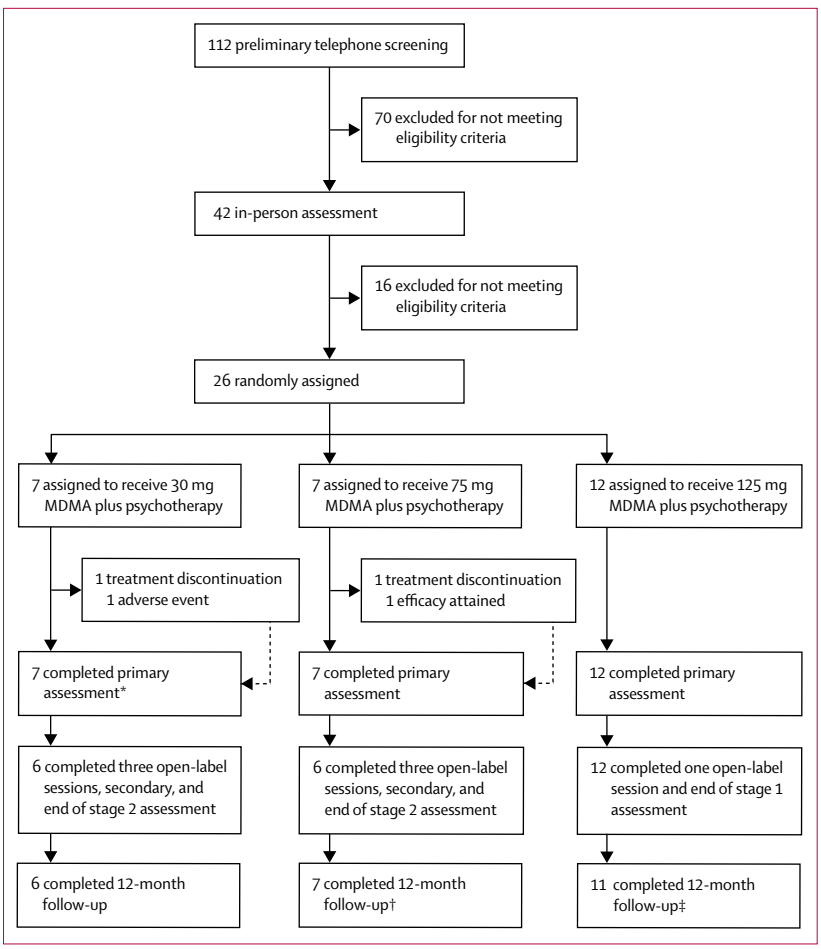


Figure 2: **Trial profile**
MDMA=3,4-methylenedioxymethamphetamine. *One participant completed one experimental session and primary endpoint assessment. †One participant discontinued treatment after one experimental session because of treatment efficacy (felt further MDMA sessions were unnecessary) but completed the primary and 12-month follow-up assessments. ‡One participant lost to follow-up.

and at least one follow-up assessment). Six (86%) of seven participants who were assigned to the 30 mg group and six (86%) of seven assigned to the 75 mg group completed the crossover open-label sessions and assessments. 24 participants completed the 12-month follow-up assessments.

The mean change in the CAPS-IV total score from baseline to 1 month after the second blinded experimental session of MDMA plus psychotherapy was –11·4 (SD 12·7) for the 30 mg group, –58·3 (9·8) for the 75 mg group, and –44·3 (28·7) for the 125 mg group (table 2; figure 3). The 75 mg (p=0·0005) and 125 mg (p=0·004) MDMA groups had significantly greater improvements in PTSD symptom severity than the 30 mg MDMA group (ANOVA for mean change in CAPS-IV total score p=0·001); no significant differences were found between the 75 mg and 125 mg groups (p=0·185). Compared with the 30 mg group, Cohen's *d* effect sizes were large: 2·8 (95% CI 1·19–4·39) for the 75 mg group and 1·1 (0·04–2·08) for the 125 mg group. At the primary endpoint (ie, after the 1-month second blinded experimental session), a larger percentage of participants in the active dose groups did not meet PTSD diagnostic criteria on CAPS-IV compared with the comparator group (six [86%] of seven participants in the 75 mg group and seven [58%] of 12 in the 125 mg group *vs* two [29%] of seven in the 30 mg group). Additionally, more participants reached a clinically significant decrease of more than 30% in CAPS-IV total score after two active doses of MDMA (all seven [100%] in the 75 mg group, eight [67%] in the 125 mg group, and two [29%] in the 30 mg group). A sensitivity analysis adjusting for baseline scores produced similar results (data not shown).

1 month after the second blinded experimental session, depression symptoms for the 125 mg group were significantly reduced compared with the 30 mg group (mean change in BDI-II score of –24·6 *vs* –4·6; p=0·0003), while comparison of the 75 mg group with the 30 mg group was not significant (–15·4 *vs* –4·6; p=0·052; table 2), with the 75 mg group showing a larger average drop from baseline (ANOVA for mean change in BDI-II scores p=0·001; figure 3). For mean change in PSQI scores (figure 3), the 75 mg group showed the greatest improvement in sleep quality followed by the 125 mg and 30 mg groups (ANOVA for mean change in PSQI scores p=0·029). *t* tests indicated superiority in the 75 mg (p=0·014) and 125 mg (p=0·022) groups compared with the 30 mg group. Post-traumatic growth followed a similar trajectory in mean PTGI scores (ANOVA for mean change in PTGI scores p<0·0001), with the active dose groups reporting significant post-traumatic growth compared with the 30 mg group (p<0·0001). Global psychological function improved (ANOVA for mean change in GAF scores p=0·004), with significantly higher functioning in the 75 mg (p=0·004) and 125 mg (p=0·002) groups than the 30 mg group. Similarly, the active dose groups had significant improvement in dissociative symptoms compared with the 30 mg group (p=0·02 for the 75 mg group *vs* 30 mg group; p=0·01 for the 125 mg group *vs* 30 mg group; ANOVA for mean change in DES-II scores p=0·026). For the NEO-PI-R, only changes in openness produced significant differences between groups (ANOVA for mean change in NEO-PI-R personality scores p=0·025), with the 75 mg group showing qualities of being more open than the 30 mg group (p=0·02).

1 month after completing two open-label sessions of 100–125 mg of MDMA in the crossover, the group that received 30 mg during blinded sessions showed reductions in symptom severity, mean change from the primary endpoint was CAPS-IV total score –27·0 (SD 17·5), and two (33%) of six participants did not meet CAPS-IV PTSD diagnostic criteria (appendix). Within-subject *t* tests comparing scores at primary and secondary endpoints showed significant improvements in mean CAPS-IV total score (p=0·01) and four (67%) of six participants attained a decrease of more than 30% in

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)	Total (n=26)
Mean age, years	39·2 (9·7)	29·1 (4·0)	40·7 (11·1)	37·2 (10·3)
Sex				
Men	5 (71%)	6 (86%)	8 (67%)	19 (73%)
Women	2 (29%)	1 (14%)	4 (33%)	7 (27%)
Ethnicity				
White	6 (86%)	4 (57%)	12 (100%)	22 (85%)
Latino or Hispanic	1 (14%)	1 (14%)	0	2 (8%)
Native American	0	1 (14%)	0	1 (4%)
Native American and white	0	1 (14%)	0	1 (4%)
Mean BMI	32·5 (4·7)	27·9 (5·4)	27·5 (3·6)	29·0 (4·8)
Occupation associated with trauma				
Military	6 (86%)	7 (100%)	9 (75%)	22 (85%)
Firefighter	1 (14%)	0	2 (17%)	3 (12%)
Police officer	0	0	1 (8%)	1 (4%)
Mean duration of PTSD, months	68·9 (15·0)	58·3 (32·3)	110·9 (85·1)	85·4 (63·9)
Pre-study therapy				
Eye movement desensitisation reprocessing	2 (29%)	0	1 (8%)	3 (12%)
Group psychotherapy	2 (29%)	2 (29%)	3 (25%)	7 (27%)
Prolonged exposure therapy	3 (43%)	1 (14%)	1 (8%)	5 (19%)
Cognitive processing therapy	0	1 (14%)	0	1 (4%)
Cognitive behavioural therapy, not otherwise specified	7 (100%)	6 (86%)	11 (92%)	24 (92%)
Psychodynamic therapy	2 (29%)	0	3 (25%)	5 (19%)
Interpersonal therapy	0	1 (14%)	0	1 (4%)
Other	5 (71%)	3 (43%)	8 (67%)	16 (62%)
None	0	0	1 (8%)	1 (4%)
Pre-study psychiatric medications				
Antidepressants	6 (86%)	7 (100%)	12 (100%)	25 (96%)
Anxiolytics	6 (86%)	5 (71%)	12 (100%)	23 (88%)
Antipsychotics	5 (71%)	2 (29%)	3 (25%)	10 (38%)
Mood stabiliser	0	0	2 (17%)	2 (8%)
Sleep aids	4 (57%)	2 (29%)	7 (58%)	13 (50%)
Stimulants	2 (29%)	4 (57%)	2 (17%)	8 (31%)
Other	2 (29%)	1 (14%)	5 (42%)	8 (31%)
Psychiatric comorbid disorders				
Major depression	5 (71%)	5 (71%)	10 (83%)	20 (77%)
Panic disorder	4 (57%)	2 (29%)	3 (25%)	9 (35%)
Generalised anxiety disorder	0	1 (14%)	1 (8%)	2 (8%)
Lifetime C-SSRS*				
Positive ideation	5 (71%)	6 (86%)	11 (92%)	22 (85%)
Serious ideation	1 (14%)	2 (29%)	5 (42%)	8 (31%)
Positive behaviour	4 (57%)	2 (29%)	5 (42%)	11 (42%)

Data are mean (SD) or n (%). Participants could have or report more than one pre-study therapy, pre-study psychiatric medication, and psychiatric comorbid disorder. MDMA=3,4-methylenedioxymethamphetamine. BMI=body-mass index. PTSD=post-traumatic stress disorder. C-SSRS=Columbia-Suicide Severity Rating Scale. *Lifetime accounts for all suicidal ideation and behaviour before this study, according to participant recall and medical records. According to the C-SSRS scoring guide, scores of 4 or 5 on the suicidal ideation category are considered serious ideation, and scores of 1 or greater are considered positive behaviour or ideation. Participants could have met criteria for more than one CSSRS category.

Table 1: **Demographics and baseline characteristics**

CAPS-IV total score (appendix). The 75 mg group did not have further significant decreases in mean CAPS-IV total score after the two open-label sessions (p=0·81), but all of the participants no longer met CAPS-IV PTSD criteria. Although CAPS-IV total scores continued to trend towards further improvement, within-subject comparison of two versus three sessions of MDMA did not yield significant differences for any measures or groups (appendix).

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)
Primary efficacy measure			
Mean CAPS-IV total score			
Baseline	87·4 (14·1)	82·4 (17·3)	89·7 (17·3)
After two experimental sessions of MDMA	76·0 (23·4)	24·1 (17·2)	45·3 (33·8)
Change†	−11·4 (12·7)	−58·3 (9·8)	−44·3 (28·7)
p value‡	NA	0·0005	0·004
Secondary efficacy measures			
Number of participants who met CAPS-IV PTSD diagnostic criteria (primary endpoint)			
Yes	5 (71%)	1 (14%)	5 (42%)
No	2 (29%)	6 (86%)	7 (58%)
Number of participants who had more than 30% decrease in CAPS-IV total score (primary endpoint)			
Yes	2 (29%)	7 (100%)	8 (67%)
No	5 (71%)	0	4 (33%)
Mean BDI-II score			
Baseline	30·4 (13·7)	24·7 (12·6)	36·6 (10·5)
After two experimental sessions of MDMA	25·9 (11·2)	9·3 (6·8)	12·0 (9·0)
Change†	−4·6 (8·8)	−15·4 (9·5)	−24·6 (10·6)
p value‡	NA	0·052	0·0003
Mean PSQI§			
Baseline	10·8 (5·7)	13·6 (4·2)	14·6 (3·6)
After two experimental sessions of MDMA	12·6 (5·2)	7·2 (4·1)	9·4 (5·1)
Change†	1·8 (2·8)	−6·4 (7·1)	−4·8 (4·1)
p value‡	NA	0·01	0·02
Mean PTGI score			
Baseline	23·9 (8·6)	29·9 (9·4)	31·5 (17·3)
After two experimental sessions of MDMA	12·3 (15·1)	66·0 (14·1)	65·2 (22·8)
Change†	−11·6 (12·2)	36·1 (12·0)	33·7 (24·0)
p value‡	NA	<0·0001	<0·0001
Mean GAF score			
Baseline	41·9 (11·8)	48·1 (9·1)	40·2 (7·2)
After two experimental sessions of MDMA	43·0 (12·8)	67·6 (6·2)	58·6 (12·1)
Change†	1·1 (4·6)	19·4 (6·1)	18·4 (14·4)
p value‡	NA	0·004	0·002
Mean DES-II score§			
Baseline	13·5 (17·7)	17·7 (9·1)	17·6 (10·7)
After two experimental sessions of MDMA	15·2 (17·4)	9·2 (10·9)	8·8 (8·0)
Change†	1·8 (0·9)	−8·6 (1·9)	−8·8 (6·2)
p value‡	NA	0·02	0·01
Mean NEO-PI-R score¶			
Neuroticism			
Baseline	62·0 (14·8)	65·3 (11·4)	75·1 (6·4)
After two experimental sessions of MDMA	60·2 (14·9)	53·6 (12·4)	58·6 (12·8)
Change†	−4·6 (5·5)	−12·0 (3·6)	−16·5 (11·8)
p value‡	NA	0·23	0·03
Extroversion			
Baseline	33·1 (9·4)	37·4 (8·9)	34·2 (8·5)

(Table 2 continues on next page)

PTSD symptoms were significantly reduced at the 12-month follow-up compared with the baseline for all MDMA groups combined (mean CAPS-IV total score of 38·8 [SD 28·1] *vs* 87·1 [16·1]; p<0·0001; table 3). Of the 24 participants who completed the 12-month follow-up, 16 (67 %) did not meet CAPS-IV PTSD criteria. On the one hand, two participants who did not meet PTSD criteria at treatment exit (after three active doses of the MDMA sessions) met PTSD diagnostic criteria at 12-month follow-up. On the other hand, three participants who met criteria at exit did not meet criteria at the 12-month follow-up.

Scores on all secondary measures at 12-month follow-up showed improvement compared with baseline (table 3). Depression symptom severity as measured on BDI-II was severe at baseline and changed to minimal by 12-month follow-up (p<0·0001). Similarly, sleep quality was vastly improved at the last endpoint as measured by PSQI (p=0·0002). Findings for post-traumatic growth (p<0·0001) and global functioning (p<0·0001) showed marked gains, and severity of dissociative symptoms was reduced (p=0·046). Compared with baseline, all NEO personality traits had significantly improved except conscientiousness (p=0·36; table 3). Two (8%) of 24 participants reported taking ecstasy once during the 12 months following the active treatment phase. At study enrolment, both of these participants had used ecstasy two times previously (6 months to 2 years before enrolment).

The treatment was well tolerated. 85 adverse events were reported by 20 participants during the study (appendix), of which four (5%) occurred before drug administration. Four (5%) of 85 were serious adverse events: three were deemed unrelated and one possibly related to study drug treatment. Serious adverse events deemed unrelated were suicidal ideation in response to life events, major depression (same participant), and appendicitis. One participant who had exhibited a premature ventricular contraction at baseline developed an acute increase in premature ventricular contractions during the third open-label session, detected on-site through routine heart rate readings. This participant had an overnight hospital stay for observation and cardiac assessment, and recovered fully without evidence for vascular or structural cardiac disease. The number of participants reporting at least one treatment-emergent adverse event was similar across groups: six (86%) of seven in the 30 mg and 75 mg groups, and eight (67%) of 12 in the 125 mg group. The most frequently reported treatment-emergent adverse events were psychiatric symptoms (table 4).

The most frequently reported expected adverse reactions during experimental sessions included anxiety, headache, fatigue, and muscle tension (table 4). Adverse reactions during 7 contact days included fatigue, anxiety, and insomnia (table 4). Most adverse reactions were mild to moderate in severity, with occurrence decreasing across the 7 days following experimental sessions.

Self-limited elevations in pulse, blood pressure, and body temperature were observed during MDMA sessions and did not require medical intervention (appendix). ANOVA of peak vital signs during blinded sessions showed a significant dose effect for systolic blood pressure (SBP; p<0·0001), diastolic blood pressure (DBP; p=0·003), and heart rate (HR; p<0·0001) but not for body temperature (p=0·095). The 125 mg group was significantly higher than the 30 mg for SBP (p<0·0001), DBP (p=0·0007), and HR (p<0·0001), and the 75 mg group was significantly higher than the 30 mg for SBP (p=0·007) and HR (p=0·018).

At all post-treatment endpoints, the percentage of participants reporting suicidal ideation and behaviour was reduced compared with baseline life-time and pre-treatment reports (table 1; appendix). During the treatment period, transient increases in suicidal ideation were observed in the 30 mg, 125 mg, and open-label groups. One participant, who had a history of suicide attempts before enrolment, was admitted to hospital for 6 days by their psychiatrist because of suicidal thoughts 13 days after their second 30 mg session. This patient subsequently completed the study. There were no treatment-emergent reports of positive suicidal behaviour.

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)
(Continued from previous page)			
After two experimental sessions of MDMA	36·0 (11·2)	46·4 (8·6)	42·2 (13·3)
Change†	2·2 (4·3)	10·0 (9·4)	8·0 (9·4)
p value‡	NA	0·17	0·22
Openness			
Baseline	48·9 (9·6)	55·6 (12·1)	57·4 (16·7)
After two experimental sessions of MDMA	49·2 (10·2)	66·0 (7·8)	59·4 (9·9)
Change†	–0·6 (9·9)	15·6 (5·3)	2·0 (10·5)
p value‡	NA	0·02	0·62
Agreeableness			
Baseline	44·7 (8·0)	33·1 (15·2)	39·8 (13·7)
After two experimental sessions of MDMA	40·6 (13·6)	33·4 (9·6)	45·7 (11·4)
Change†	–1·2 (8·4)	5·4 (8·0)	5·9 (4·9)
p value‡	NA	0·13	0·05
Conscientiousness			
Baseline	41·3 (9·9)	53·6 (18·3)	41·3 (13·5)
After two experimental sessions of MDMA	39·8 (6·8)	56·4 (10·1)	47·8 (10·0)
Change†	–3·2 (7·9)	2·4 (15·0)	6·5 (13·4)
p value‡	NA	0·50	0·17

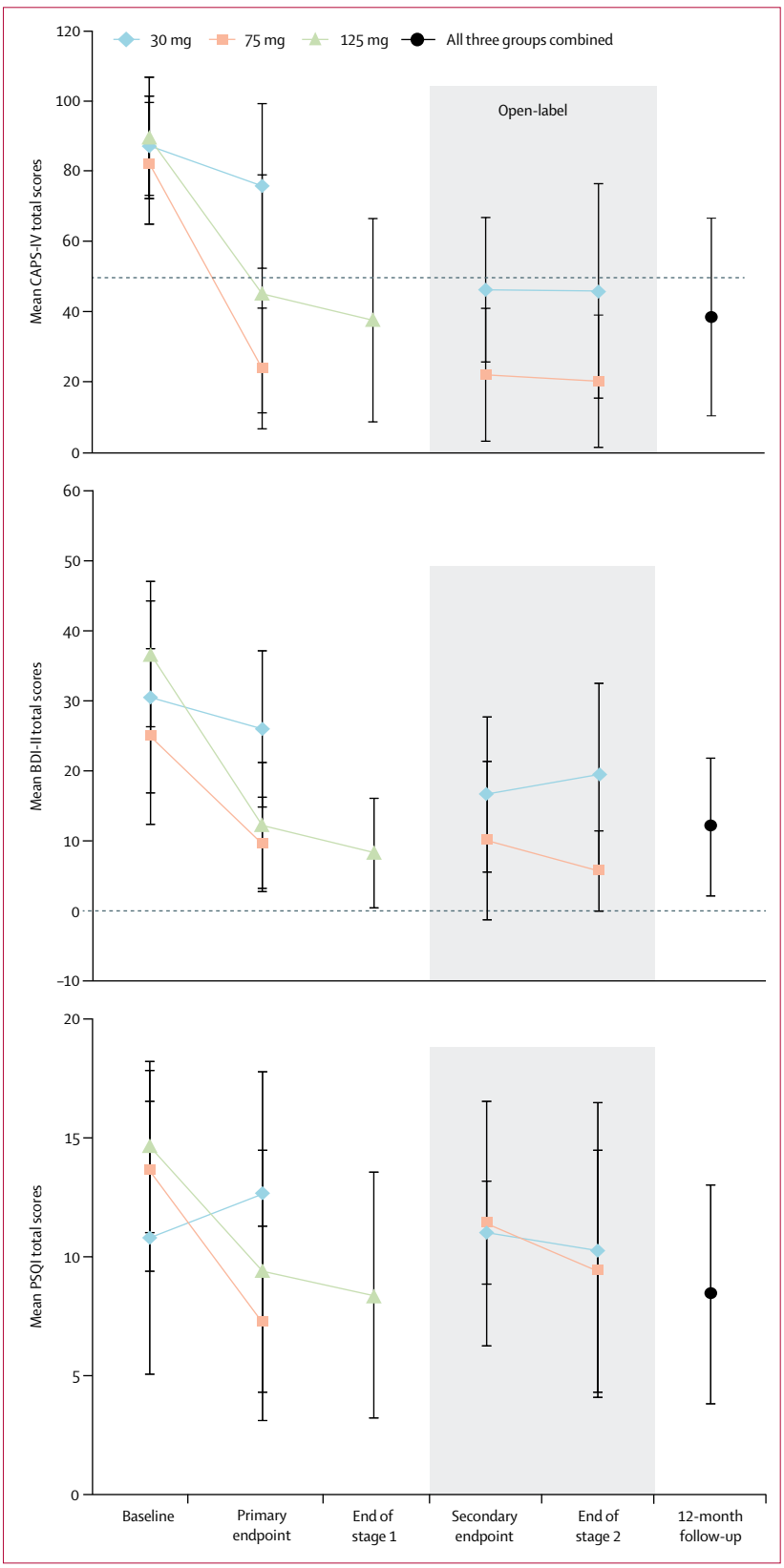
Data are mean (SD) or n (%). MDMA=3,4-methylenedioxymethamphetamine. CAPS-IV=Clinician-Administered PTSD Scale. PTSD=post-traumatic stress disorder. NA=not applicable. BDI-II=Beck Depression Inventory-II. PSQI=Pittsburgh Sleep Quality Index. PTGI=Post-Traumatic Growth Inventory. GAF=Global Assessment of Functioning. DES-II=Dissociative Experiences Scale II. NEO-PI-R=Neuroticism-Extroversion-Openness Personality Inventory-Revised. *All outcomes are based on the intention-to-treat population. †Change from baseline. ‡Compared with 30 mg MDMA. §Reduced sample size because of protocol amendment (PSQI: n=5 for 30 mg group, n=5 for 75 mg group, and n=10 for 125 mg group. DES-II: n=3 for 30 mg group, n=3 for 75 mg group, and n=6 for 125 mg group). ¶n=5 for the NEO-PI-R sample size of the 75 mg group at the primary endpoint.

Table 2: **Outcome measures* at the primary endpoint of 1 month after the second experimental MDMA session**

Discussion

MDMA-assisted psychotherapy with 75 mg or 125 mg resulted in marked improvement of PTSD symptoms in veterans and first responders with chronic PTSD who had failed previous treatment. This study extends findings of significant results combining MDMA with the same manualised psychotherapy for treating crime-related PTSD,[12] and supports the durability of symptomatic improvement seen in a previous report.[14] Participants in the comparator group of 30 mg receiving the same psychotherapy had significantly less symptom remission than the active dose groups of 75 mg and 125 mg, indicating that adequate doses of MDMA potentiate the effects of psychotherapy. An unexpected finding was that the 75 mg dose led to larger decreases in CAPS-IV total score than the 125 mg dose. This difference might have been due to chance in this small sample size or might be due to other reasons. For example, participants of the 125 mg group had a higher mean baseline depression score than the other groups, and therefore could have been harder to treat. Another possible explanation is that the 75 mg dose might have allowed for more focused processing of traumatic experiences than the 125 mg dose, and might be the optimal dose for at least some patients. Phase 3 trials will use a flexible dose range of 80–120 mg MDMA, and will provide further information about variables that contribute to response.

Results from measures of depression and sleep quality parallel findings from CAPS-IV, providing further evidence of benefits of this treatment. Severity of depression symptoms was significantly reduced for the 125 mg group compared with the 30 mg group; however, this reduction was not significant for the 75 mg group compared with the 30 mg group. Sleep quality and dissociative symptoms also significantly improved for both active dose groups compared with the control dose group. Additionally, there were gains in psychological, occupational, and social functioning for participants treated with active doses of MDMA, and similar to the improvements in PTSD symptoms, these gains continued to grow in the year following treatment. Increased scores on the PTGI indicate that perceptions of self, others, and life events were reframed during the therapeutic processing, suggesting that treatment effects went beyond reductions in PTSD and mood symptoms to include psychological growth. Compared with the 30 mg group, change in personality traits showed statistically significant reductions in neuroticism in the 125 mg group and increases in openness in the 75 mg group. Although many personality theorists would argue that personality traits are relatively stable constructs throughout much of adulthood and are not subject to change,



evidence suggests that certain personality features are associated with traumatic experience.[25] MacLean and colleagues[26] found an effect of psilocybin on changes in one of the five broad domains of personality (openness) measured by the NEO-PI-R, and speculated about the potential clinical application and therapeutic benefit of change in personality variables as a result of pharmacologically induced "mystical experiences". We have previously found persistent personality changes in openness and neuroticism following MDMA treatment, providing support for the notion that the effect of MDMA-assisted psychotherapy extends beyond effects on specific PTSD symptomatology,[27] and fundamentally alters personality structure. In the current study, the fact that participants exhibited long-term changes in personality traits at 12-month follow-up that included a reduction in neuroticism and an increase in agreeableness, openness, and extroversion further suggests that combining MDMA with psychotherapy can shift aspects of personality that were assumed to be stable across time. These pervasive therapeutic effects raise interesting questions for future research into other possible indications for MDMA-assisted psychotherapy, and about whether MDMA effects might be better understood as equipping people to face a range of psychological challenges effectively than as narrowly targeting specific diagnoses.

After participants in the 30 mg group crossed over to receive two open-label sessions of 100–125 mg MDMA, mean CAPS-IV total score showed an additional 27-point average decline, suggesting that the same psychotherapy alone was not nearly as effective without a sufficient dose of MDMA. After the third open-label session, the mean change in CAPS-IV total score (–27 points) and the percentage of participants no longer meeting criteria for PTSD (50%) in this group was less than the other groups; however, the proportion of participants with more than a 30% decrease in CAPS-IV total score was more than the 125 mg group (67% *vs* 50%). The fact that the total decrease in mean CAPS-IV score at the primary endpoint was less for the 30 mg group could mean this group was more difficult to treat than the 75 mg and 125 groups; however, it is also of note that low-dose MDMA appears to have a counter-therapeutic effect as reported by Oehen and colleagues,[13] and as reflected in the fact that a previous study using inactive placebo with the same psychotherapy showed a greater decrease in mean CAPS-IV total score than the 30 mg group showed

Figure 3: **Mean CAPS-IV, BDI-II, and PSQI scores over time from baseline to endpoints (intention-to-treat population)**
Error bars are SDs. The dotted line at CAPS-IV total score 50 was one of the inclusion criteria for study enrolment. Assessments for graphs selected on the basis of representation of PTSD severity and most common associated symptoms—ie, depression and sleep disturbance. CAPS-IV=Clinician Administered PTSD Scale. PTSD=post-traumatic stress disorder. BDI-II=Beck Depression Inventory-II. PSQI=Pittsburgh Sleep Quality Index.

in the current study (–33 *vs* –11·4).[12] Other factors might also have influenced response in the control groups across these studies with small samples. The study was not designed to determine whether response is greater after two versus three sessions but results suggest that a high degree of improvement can be reached after two sessions. Future studies should evaluate the degree of added long-term benefit that might occur from three versus two sessions. The long-term follow-up results showing significant CAPS-IV total score reductions 12 months after the last MDMA-assisted treatment make it unlikely that the more immediate results were simply due to placebo effect or lingering expectancy effects of having received MDMA.

MDMA was well tolerated with low treatment discontinuation (7·7%) that did not correlate with dose. Vital signs transiently increased in a dose-dependent manner during experimental sessions, and returned to approximate baseline values at the session end. Incidence of expected reactions and adverse events differed little across groups, although known acute side-effects of MDMA, such as jaw clenching and perspiration, did occur at higher frequency with active doses. Most events were mild to moderate, with many of the psychiatric symptoms possibly attributable to PTSD. Suicidal ideation was similar across groups. No suicidal behaviour occurred during treatment, suggesting that MDMA-assisted psychotherapy did not potentiate the risk of suicide. Indications of suicidal ideation were lower after completing the treatment. When MDMA is administered in a controlled clinical setting, the liability for subsequent abuse or compulsive seeking of ecstasy is presumed low, as shown in the current trial. Participants who were naive to ecstasy before study participation did not report taking ecstasy after receiving MDMA in the trial. Two participants reported taking ecstasy once during the 12-month follow-up, but both had taken the drug before study enrolment. Overall safety data support a favourable risk-to-benefit ratio for limited doses of MDMA for treating a population with PTSD.[12–14]

This model of treatment is different to most pharmacological interventions, in that its effectiveness appears to be mediated through pharmacological effects augmenting meaningful psychotherapeutic experiences. MDMA might attenuate response to anxiety-provoking thoughts or feelings during recall of trauma memories by reducing activity in the amygdala[28,29] and insular cortex,[30] and simultaneously improve top-down modulation of thoughts and emotions by increasing activity in the prefrontal cortex.[29] Increased functional connectivity between the amygdala and hippocampus during MDMA administration[28] suggests that reconsolidation of traumatic memories might occur, rendering them less activating during ordinary states.[31] Conversely, veterans with symptomatic PTSD have shown decreased resting state functional connectivity between the amygdala and hippocampus.[32] MDMA modulates emotional memory circuits dysfunctional in PTSD,[33] and engages neural networks illustrated to be important for other trauma processing therapies.[34] By increasing prosocial and empathetic feelings, MDMA might improve therapeutic

	30 mg MDMA plus psycho-therapy (n=7)	75 mg MDMA plus psycho-therapy (n=7)	125 mg MDMA plus psycho-therapy (n=12)	Total (n=26)	p value†
Primary efficacy measure					
Mean CAPS-IV total score					
Baseline	87·4 (14·1)	82·4 (17·3)	89·7 (17·3)	87·1 (16·1)	..
12-month follow-up	52·7 (41·2)	28·3 (23·0)	37·8 (21·4)	38·8 (28·1)	<0·0001
Secondary efficacy measures					
Number of participants who met CAPS-IV PTSD diagnostic criteria (12-month)					
Yes	3 (50%)	2 (29%)	3 (27%)	8 (33%)	..
No	3 (50%)	5 (71%)	8 (72%)	16 (67%)	NA
Mean BDI-II score					
Baseline	30·4 (13·7)	24·7 (12·6)	36·6 (10·5)	31·7 (12·5)	..
12-month follow-up	15·2 (13·4)	11·0 (9·3)	10·5 (8·6)	11·8 (9·9)	<0·0001
Mean PSQI‡					
Baseline	10·8 (5·7)	13·6 (4·2)	14·6 (3·6)	13·4 (4·4)	..
12-month follow-up	9·8 (4·3)	7·4 (4·6)	8·4 (5·0)	8·4 (4·6)	0·0002
Mean PTGI score					
Baseline	23· 9 (8·6)	29·9 (9·4)	31·5 (17·3)	29·0 (13·5)	..
12-month follow-up	49·0 (32·2)	74·1 (15·0)	78·2 (15·1)	69·7 (23·1)	<0·0001
Mean GAF score					
Baseline	41·9 (11·8)	48·1 (9·1)	40·2 (7·2)	42·8 (9·4)	..
12-month follow-up	54·0 (20·2)	66·7 (14·8)	64·8 (12·8)	62·7 (15·6)	<0·0001
Mean DES-II score‡					
Baseline	13·5 (17·7)	17·7 (9·1)	17·6 (10·7)	16·6 (11·3)	..
12-month follow-up	10·5 (1·8)	9·6 (6·3)	12·5 (12·8)	11·2 (8·7)	0·046
Mean NEO-PI-R score§					
Neuroticism					
Baseline	62·0 (14·8)	65·3 (11·4)	75·1 (6·4)	68·9 (11·7)	..
12-month follow-up	57·0 (12·2)	61·1 (8·4)	57·2 (9·3)	58·3 (9·6)	<0·0001
Extroversion					
Baseline	33·1 (9·4)	37·4 (8·9)	34·2 (8·5)	34·8 (8·7)	..
12-month follow-up	37·3 (6·8)	46·4 (6·9)	45·4 (11·0)	43·7 (9·4)	0·0002
Openness					
Baseline	48·9 (9·6)	55·6 (12·1)	57·4 (16·7)	54·6 (13·9)	..
12-month follow-up	51·0 (11·5)	65·0 (7·5)	60·5 (15·6)	59·5 (13·3)	0·015
Agreeableness					
Baseline	44·7 (8·0)	33·1 (15·2)	39·7 (13·7)	39·3 (13·1)	..
12-month follow-up	43·8 (9·8)	38·6 (11·6)	47·4 (13·0)	43·9 (12·0)	0·007
Conscientiousness					
Baseline	41·3 (9·9)	53·6 (18·3)	41·2 (13·5)	44·6 (14·7)	..
12-month follow-up	43·5 (5·7)	53·1 (11·5)	46·9 (10·8)	47·9 (10·3)	0·36

Data are mean (SD) or n (%). MDMA=3,4-methylenedioxymethamphetamine. CAPS-IV=Clinician Administered PTSD Scale. PTSD=post-traumatic stress disorder. NA=not applicable. BDI-II=Beck Depression Inventory-II. PSQI=Pittsburgh Sleep Quality Index. PTGI=Post-Traumatic Growth Inventory. GAF=Global Assessment of Functioning. DES-II=Dissociative Experiences Scale II. NEO-PI-R=Neuroticism-Extroversion-Openness Personality Inventory-Revised. *All outcomes are based on the intention-to-treat population. †Within-subject *t* tests with groups combined. ‡Reduced sample size because of protocol amendment (PSQI: n=4 for 30 mg group, n=5 for 75 mg group, and n=10 for 125 mg group. DES-II: n=3 for 30 mg group, n=3 for 75 mg group, and n=5 for 125 mg group). §n=11 for NEO-PI-R sample size of the 125 mg group at 12-month follow-up.

Table 3: **Outcome measures at 12-month follow-up***

	30 mg MDMA plus psychotherapy (n=7)	75 mg MDMA plus psychotherapy (n=7)	125 mg MDMA plus psychotherapy (n=12)	Total (n=26)
Most reported reactions during experimental sessions*				
Anxiety	4 (57%)	6 (86%)	11 (92%)	21 (81%)
Fatigue	5 (71%)	4 (57%)	7 (58%)	16 (62%)
Headache	5 (71%)	5 (71%)	8 (67%)	18 (69%)
Jaw clenching or tight jaw	0	4 (57%)	9 (75%)	13 (50%)
Reduced appetite	3 (43%)	4 (57%)	8 (67%)	15 (58%)
Muscle tension	4 (57%)	3 (43%)	9 (75%)	16 (62%)
Perspiration	2 (29%)	2 (29%)	5 (42%)	9 (35%)
Restlessness	4 (57%)	5 (71%)	3 (25%)	12 (46%)
Sensitivity to cold	4 (57%)	4 (57%)	6 (50%)	14 (54%)
Most reported reactions during 7 days of contact*				
Anxiety	4 (57%)	5 (71%)	10 (83%)	19 (73%)
Fatigue	6 (86%)	7 (100%)	10 (83%)	23 (88%)
Insomnia	5 (71%)	3 (43%)	10 (83%)	18 (69%)
Need more sleep	6 (86%)	6 (86%)	9 (75%)	21 (81%)
Headache	2 (29%)	3 (43%)	7 (58%)	12 (46%)
Muscle tension	2 (29%)	3 (43%)	7 (58%)	12 (46%)
Increased irritability	4 (57%)	2 (29%)	6 (50%)	12 (46%)
Lack of appetite	2 (29%)	1 (14%)	6 (50%)	9 (35%)
Difficulty concentrating	2 (29%)	0	5 (42%)	7 (27%)
Low mood	3 (43%)	0	3 (25%)	6 (23%)
Psychiatric treatment-emergent adverse events†				
Anxiety	1 (14%)	0	1 (8%)	2 (8%)
Flashbacks	0	0	1 (8%)	1 (4%)
Low mood	2 (29%)	0	0	2 (8%)
Negative thoughts	1 (14%)	0	0	1 (4%)
Suicidal ideation	1 (14%)	0	0	1 (4%)
Tic	0	0	1 (8%)	1 (4%)
Trichotillomania	1 (14%)	0	0	1 (4%)

Data are n (%). MDMA=3,4-methylenedioxymethamphetamine. *Frequency of participants who reported an expected, spontaneously reported reaction collected during and 7 days following blinded experimental sessions one and two. †Frequency of participants who self-reported psychiatric adverse events after first drug administration until the day before experimental session three.

Table 4: **Treatment-emergent adverse events and expected reactions during two MDMA sessions and 7 days following these sessions**

alliance and engagement with difficult psychological material. Because this study was not designed to explore mechanisms of action, the importance of these pharmacological effects and neural correlates remains speculative but is consistent with investigators' observations during research sessions.

Possible mechanisms should also take into account the interactions between drug effects and participants' psychological experiences. The manualised approach to psychotherapy used[17] includes elements that contribute to the safety and efficacy of MDMA as an adjunct to psychotherapy: careful medical and psychological screening, preparing participants for the MDMA experience and the treatment, a largely non-directive approach that includes periods of inner focus alternating with periods of interaction with male and female co-therapists, and close follow-up to support integration of the MDMA experience. Previous reports comparing MDMA with inactive placebo,[12] and the current study using low-dose MDMA as a comparator, show that this model of psychotherapy without an active dose of MDMA does lead to improvement in CAPS-IV total score, but the combined effect of the psychotherapy in conjunction with active doses of MDMA is significantly larger.

This study has limitations regarding the design and small sample size. Most participants were white men. Maintaining the study blind was only partially accomplished by using low-dose MDMA instead of inactive placebo. The co-therapists guessed dose assignment incorrectly for 40·7–42·6% of blinded sessions and participants guessed incorrectly for 53·7%, suggesting some success in blinding, although most incorrect guesses were between active doses, not between an active dose and low dose, so we cannot rule out some bias from this limitation. There appears to be a threshold effect beyond which MDMA catalyses an effective therapeutic process, and participants and therapists can distinguish the active drug effects from subthreshold effects of low-dose MDMA or inactive placebo. To prevent observer expectancy effects and minimise bias, an observer blind was used by having masked independent outcome raters who were not present during therapy sessions. Widely accepted evidence for the effectiveness of trauma-based psychotherapy for PTSD exists, yet it is impossible to effectively blind psychotherapy trials.[6] Similar limitations to blinding exist for MDMA and other drugs with prominent psychoactive effects. A limitation of the 12-month follow-up results is that after the primary endpoint, the 30 mg dose and 75 mg dose groups crossed over to receive a full dose of MDMA; therefore, no control group for comparison at 12 months existed. Additionally, 12 participants were taking psychiatric medications, although none specifically for an indication of PTSD, at the long-term follow-up visit.

This trial provides further evidence that MDMA-assisted psychotherapy can be used safely and effectively for treating patients with chronic PTSD. This novel approach to pharmacotherapy offers a means to accelerate substantially the therapeutic process with a short-acting psychoactive compound administered only a few times at monthly intervals in conjunction with a course of psychotherapy designed to maximise the safety and efficacy of drug administration. Promising phase 2 efficacy and safety results have now been shown in six studies.[11] If findings are validated in MAPS' phase 3 clinical trials, set to start in 2018,[11] MDMA-assisted psychotherapy might become a viable, FDA-approved treatment option for PTSD by 2021.

Contributors

SH is responsible for the integrity of the data and accuracy of data analyses. MCM, ATM, LJ, BY-K, AE, and RD conceived and designed the study. All authors acquired, analysed, and interpreted all data. MCM, AAF, and LJ drafted the manuscript. All authors critically revised the manuscript. RD obtained funding. MCM and ATM supervised the study.

Declaration of interests
MCM has received research funds from the Multidisciplinary Association for Psychedelic Studies (MAPS) Public Benefit Corporation as a clinical investigator and clinical trial medical monitor, as well as for training and supervision of research psychotherapists. ATM has received research funds from MAPS Public Benefit Corporation as a clinical investigator and for training and supervision of research psychotherapists. AAF, LJ, and AE are full-time employees of MAPS Public Benefit Corporation. MW and JW have received research funds to do study assessments. JH declares no competing interests. SH has received research funds from MAPS Public Benefit Corporation for his role as a biostatistician. BY-K and RD are full-time employees of MAPS.

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ORIGINAL INVESTIGATION

MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials

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Abstract

Background Posttraumatic stress disorder is a prevalent mental health condition with substantial impact on daily functioning that lacks sufficient treatment options. Here we evaluate six phase 2 trials in a pooled analysis to determine the study design for phase 3 trials of MDMA-assisted psychotherapy for PTSD.

Methods Six randomized, double-blind, controlled clinical trials at five study sites were conducted from April 2004 to February 2017. Active doses of MDMA (75–125 mg, $n = 72$) or placebo/control doses (0–40 mg, $n = 31$) were administered to individuals with PTSD during manualized psychotherapy sessions in two or three 8-h sessions spaced a month apart. Three non-drug 90-min therapy sessions preceded the first MDMA exposure, and three to four followed each experimental session.

Results After two blinded experimental sessions, the active group had significantly greater reductions in CAPS-IV total scores from baseline than the control group [MMRM estimated mean difference (SE) between groups − 22.0 (5.17), $P < 0.001$]. The between-group Cohen's d effect size was 0.8, indicating a large treatment effect. After two experimental sessions, more participants in the active group (54.2%) did not meet CAPS-IV PTSD diagnostic criteria than the control group (22.6%). Depression symptom improvement on the BDI-II was greatest for the active group compared to the control group, although only trended towards significant group differences [MMRM, estimated mean difference (SE) between groups − 6.0 (3.03), $P = 0.053$]. All doses of MDMA were well tolerated, with some expected reactions occurring at greater frequency for the active MDMA group during experimental sessions and the 7 days following.

Conclusions MDMA-assisted psychotherapy was efficacious and well tolerated in a large sample of adults with PTSD. These studies supported expansion into phase 3 trials and led to FDA granting Breakthrough Therapy designation for this promising treatment.

Trial registration ClinicalTrials.gov Identifier: NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610.

Keywords MDMA · MDMA-assisted psychotherapy · Posttraumatic stress disorder · Anxiety · Psychedelic

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Introduction

Posttraumatic stress disorder (PTSD) is a serious debilitating disorder with lifetime prevalence estimated at nearly 4% globally and over 8% in the USA (Kilpatrick et al. 2013; Koenen et al. 2017). Symptoms of PTSD include intrusive thoughts and memories, negative effects on cognition and mood, hyperarousal and reactivity, and avoidance that do not remit for at least 1 month subsequent to exposure to a traumatic event (Koenen et al. 2017). Individuals with PTSD may experience a substantial reduction in quality of life and relationships, and the disability resulting from PTSD can have further negative consequences such as obesity (Scott et al. 2008), hypertension (Kibler et al. 2009), comorbid mental health conditions, and suicidality (Dorrington et al. 2014; Tarrier and Gregg 2004). In addition to these profound costs to individuals with PTSD, the disorder also exerts a substantial economic toll through lost productivity and treatment costs (Marshall et al. 2000).

Widely used treatments for PTSD include psychotherapies and medications. A recent review identified trauma-focused psychotherapies as first-line treatments for PTSD (Lee et al. 2016); however, while a substantial proportion of individuals with PTSD respond to psychotherapies [e.g., cognitive processing therapy (Monson et al. 2006; Resick et al. 2008) and prolonged exposure therapy (Foa et al. 2007)], these therapies may be difficult to access and are ineffective for many (Koenen et al. 2017; Steenkamp et al. 2015). A variety of medications have also been used to address PTSD symptoms, but only two drugs—sertraline and paroxetine—are approved by the FDA for PTSD. Extant pharmacotherapies, however, are ineffective for many individuals with PTSD, with an estimated 40–60% of patients not responding adequately (Bradley et al. 2005; Brady et al. 2000; Steenkamp et al. 2015). They may have problematic side effects and generally require long-term use to maintain effectiveness (Lee et al. 2016). In sum, the sizable proportion of cases of PTSD are persistent (Koenen et al. 2017) and the shortcomings of currently available treatments make the development of novel PTSD treatments a research priority.

A promising approach to the treatment of PTSD is the combination of psychotherapy with pharmacotherapy using 3,4-methylenedioxymethamphetamine (MDMA). Interest in the therapeutic potential of MDMA for trauma-related psychopathology developed in the context of the broader potential for MDMA to catalyze psychotherapeutic processes by facilitating communication and connection between therapists and patients (Nichols 1986). MDMA was first synthesized in 1912 by Merck, but it was not until the early 1970s that MDMA was first used in combination with psychotherapy. Case reports from that period described therapeutic benefits, although no clinical trials were conducted at that time. Recreational use of "Ecstasy," tablets purported to contain MDMA, became popular in the 1980s, leading to its classification as a Schedule 1 controlled substance in 1985. The scheduling of MDMA made its use in therapy illegal and created obstacles to clinical research. A non-profit organization, the Multidisciplinary Association for Psychedelic Studies (MAPS), filed a Drug Master File (DMF) application in 1986, followed by an Investigational New Drug (IND) application in 2001, embarking on the FDA drug development process to study the safety and efficacy of MDMA as an adjunct to psychotherapy for PTSD (Greer and Tolbert 1986; Grof 2001; Mithoefer 2011, 2017; Mithoefer et al. 2018).

After nonclinical toxicity studies and an investigator-initiated phase 1 study of MDMA were completed (Frith et al. 1987; Grob et al. 1996, 1998), six phase 2 randomized trials of MDMA-assisted psychotherapy for treatment of PTSD were conducted from 2004 to 2017. Active doses of MDMA (75–125 mg) or control doses of inactive placebo or low-dose MDMA (25–40 mg) were combined with manualized inner-directed psychotherapy (Mithoefer 2017) in which participants were supported by a male and female therapy team (Mithoefer et al. 2011, 2018). The therapeutic model described in the Treatment Manual was based upon initial work with classic psychedelics (Grof 2001; Mithoefer 2017) and early reports of MDMA in a therapeutic setting (Greer and Tolbert 1986). Four of these MAPS-sponsored studies have been published (Mithoefer et al. 2011, 2013, 2018; Oehen et al. 2013; Ot'alora et al. 2018), and all six studies demonstrated acceptable safety and promising efficacy results. The MDMA doses selected for phase 2 trials (control—0 mg, 25 mg, 30 mg, 40 mg; active—75 mg, 100 mg, 125 mg) were based on tolerability and subjective effects reported in several prior phase 1 studies (Cami et al. 2000; de la Torre et al. 2000; Grob et al. 1998; Harris et al. 2002; Liechti et al. 2001). Low doses (25 mg, 30 mg, 40 mg) produce some changes in subjective effects that could presumably enhance blinding as an active placebo but would be inadequate for a therapeutic response (Harris et al. 2002). The FDA, after reviewing all available data in 2016, granted Breakthrough Therapy Designation in 2017 and approved the designs of two phase 3 trials that started in 2018.

To optimize the design of the phase 3 trials, we pooled data from six phase 2 trials that had similar study objectives and designs. We aimed to determine how many MDMA sessions are needed to achieve a clinically significant response, what demographic and other baseline variables might impact outcomes, which safety parameters are essential, the optimal dose, and how best to minimize bias and enhance blinding. To that end, the aim of this paper is to present pooled data from randomized clinical trials at different study sites that evaluated the efficacy and safety profile of MDMA-assisted psychotherapy among individuals with PTSD from a range of causes.

Methods

Setting

Six randomized, double-blind phase 2 studies took place at five sites. The sites were located in the USA (MP-1, MP-8, MP-12), Canada (MP-4), Switzerland (MP-2), and Israel (MP-9). Five sites were private practices and one was a psychiatric clinic. Data were collected from April 2004 to March 2017. Studies were approved by the Western-Copernicus Institutional Review Board (Research Triangle or Cary, NC; MP-1, MP-8, MP-12), IRB Services/Chesapeake (Aurora ON; MP-4), Ethics Committee of Solothurn (Switzerland; MP-2), and Helsinki Committee of Beer Yaakov Hospital (Israel; MP-9).

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Participants

Participants were recruited through internet advertisements, referrals by health professionals, and by word of mouth. Candidates had chronic PTSD with symptoms lasting longer than 6 months and Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) scores ≥ 50 (all studies except MP-4) or ≥ 60 (MP-4) upon enrollment (see eTable 1 for individual study criteria). Studies enrolled men and women, including civilians and veterans/first responders, aged 18 and older with previous inadequate response to at least one pharmacotherapy and/or psychotherapy. An inadequate response to previous treatment was concluded if participants had a CAPS-IV total score indicating moderate to extreme PTSD at screening.

Participants underwent extensive screening by independent examiners, including psychological assessments, physical examinations, laboratory testing, and ECG to identify any possible contraindications to receiving MDMA. The Structured Clinical Interview for DSM-IV Axis I Disorders—Research Version (SCID-I-RV) or the SCID-II was used during screening to detect comorbid disorders, and medical and therapy records from outside providers were reviewed. Participants were not excluded for meeting criteria for anxiety disorders or depression but were excluded if they met criteria for past or current psychotic disorder or Bipolar Disorder 1, or for current borderline personality disorder, or eating disorder with active purging. Other exclusion criteria included significant medical diagnoses (contraindications for MDMA), pregnancy or lactation, and weight under 48 kg. Cardiovascular or cerebrovascular disease was excluded, except in one study where candidates with well-controlled hypertension and no other evidence of vascular disease could enroll after additional screening with nuclear stress test and carotid ultrasound. All therapists maintained a Basic Life Support certification, and a study physician was available by telephone throughout the study. In order to be enrolled, individuals had to meet all inclusion/exclusion criteria and agree to comply with all planned study visits. All participants confirmed comprehension of study procedures and gave written informed consent.

Participants could not have a diagnosis of substance abuse disorders within 60 days of screening for five studies and within 6 months for one study. Psychiatric medications were tapered and discontinued prior to commencing experimental sessions. Anxiolytics and sedative hypnotics were used as-needed between experimental sessions.

Protocols and treatments

After screening and enrollment, participants were randomized through a web-based system (MP-8, MP-12) or a list generated by a blinded randomization monitor (MP-1, MP-2, MP-4, MP-9) to receive blinded doses of placebo/control (0 mg placebo; 25 mg, 30 mg, or 40 mg MDMA) or active doses of MDMA (75 mg, 100 mg, or 125 mg MDMA) at approximately 1:2 ratio. Doses were administered during two 8-h psychotherapy sessions spaced 3–5 weeks apart. The initial dose was followed approximately 1.5–2.5 h later by an optional supplemental dose equal to half the initial dose. Participants could accept or decline the supplemental dose, and could discuss the choice with the therapy team. The team could withhold the supplemental dose if there were contraindicating circumstances. Participants underwent two to three non-drug 90-min therapy sessions prior to the first experimental session. Fifty participants who received 100 mg or 125 mg had a third experimental session, either open label or blinded depending on the study, and one 75 mg participant had a blinded third session before a protocol amendment changed the crossover to occur after two sessions. The control groups subsequently had the option to receive two to three open-label sessions with active dose MDMA in a crossover segment (data not shown). MDMA was synthesized by David Nichols at Purdue University. Gelatin capsules were compounded with lactose to produce equivalent-weight capsules across dose groups.

The same male/female therapy team was present for all therapy sessions for a given participant. There were 18 therapy teams across the six studies. All but one team (MP-2) were trained in the MAPS Therapy Training Program based on the method described in the MDMA-assisted Psychotherapy Treatment Manual (Mithoefer 2017). The method includes periods of introspection alternating with periods of communication between therapists and the participant. The method is aimed at allowing participants to revisit traumatic experiences while staying emotionally engaged even during intense feelings of anxiety, pain, or grief without feeling overwhelmed. The relatively non-directive approach is intended to allow for processing of other psychological, interpersonal, or behavioral

aspects of the participants' lives that are likely to arise spontaneously in addition to processing the traumatic memories that led to PTSD.

Experimental sessions took place in a designated area that contained a futon or sofa, as well as artwork or other objects intended to make the space esthetically pleasing. Participants had the option of wearing eye shades and listening to mostly instrumental music during the parts of experimental sessions when they were focused inward. After the 8-h experimental sessions, participants remained at the study site overnight with a supportive attendant. On the following day, they met with the therapists in a 90-min integration session to address and process material that arose during the experimental session. Two to three more integration sessions occurred during the month after each experimental session. For 7 days following each experimental session, the therapy team checked in with the participants in brief telephone calls to assess wellbeing and safety.

Assessments

Assessments were administered at baseline and at follow-up visits occurring 1 to 2 months after the second and third experimental sessions and at additional time points in some studies. Blinded independent raters not present during therapy sessions administered the CAPS-IV. Safety data were collected throughout treatment. Here, we present a limited set of assessments to support the rationale of this paper.

Primary outcome

The CAPS-IV is a semi-structured interview addressing PTSD symptom clusters (re-experiencing, avoidance, negative mood or cognition, and increased arousal) as recognized by DSM-IV (Blake et al. 1995; Nagy et al. 1993; Weathers et al. 2001). The CAPS-IV contains frequency and intensity scores for each of the three symptom clusters that are summed to produce a total severity score, the primary outcome for these studies. The CAPS-IV has a dichotomous diagnostic score assigned on the basis of meeting PTSD diagnostic criteria.

Secondary outcome

The Beck Depression Inventory—II (BDI-II), an established 21-item measure of self-reported depression symptoms (Beck et al. 1996), was administered in four of the six studies (MP-4, MP-8, MP-9, and MP-12). Responses are made on a four-point Likert scale and summed to produce an overall score.

Safety outcomes

Safety was assessed by tracking the rates of spontaneously reported reactions (subset of adverse events (AEs) that could be expected based on findings from published studies in healthy volunteers) during experimental sessions and 7 days following, and by recording treatment-emergent AEs (TEAEs), which were not collected on the spontaneously reported reactions list, or were reactions that continued for 7 days or more after experimental sessions. Blood pressure and heart rate were measured in intervals of 15 to 30 min, and body temperature every 60 to 90 min during experimental sessions. Suicidal ideation and behavior were collected at all visits and twice during the 7 days of contact in four of the six studies (MP-4, MP-8, MP-9, and MP-12) using the clinician-administered Columbia Suicide Severity Rating Scale (C-SSRS) (Posner et al. 2007, 2011), a structured interview addressing presence and intensity of suicidal ideation and behavior. Participants completed the Paced Auditory Serial Addition Task (PASAT) (Gronwall 1977) and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1998) at baseline and 2-month follow-up to determine whether changes in cognitive function had occurred after two sessions with placebo dose or active dose MDMA in specific studies (MP-1, MP-4, and MP-12).

Statistical analysis

Data were pooled across the six studies. Participants who received MDMA (75, 100, 125 mg) were combined into an active dose group; participants who received MDMA (0, 25, 30, 40 mg) were combined for the control group. The modified intent-to-treat set included randomized participants who completed at least one blinded experimental session and a post-baseline assessment. Missing data were not imputed. The safety set included all participants exposed to at least one dose of study drug or placebo.

Group differences in baseline characteristics and demographics were evaluated with χ^2 tests or independent-samples t tests. The primary efficacy evaluation was made with a mixed-effect repeated measure model (MMRM) on change in CAPS-IV total score from baseline to post second experimental session endpoint, and the post third experimental endpoint. The base model included treatment (active/control), baseline CAPS-IV score, and study as a fixed effect, and participant was specified as a random effect. To assess the relationship between outcome measures and age, PTSD duration, sex, race, and prior self-reported "ecstasy" use (substances assumed to contain MDMA), these variables were added to the base model one at a time. BDI-II scores were analyzed the same way. AEs were categorized with the Medical Dictionary for Regulatory Activities (MedDRA) in System Organ Classes and preferred terms. AEs, reactions, and suicidal ideation and behavior were summarized descriptively. Independent-samples t tests compared peak vital signs during experimental sessions between groups. Between-group effect size was calculated with Cohen's d (Kadel and Kip 2012). SAS software version 9.3 (SAS Institute Inc., Cary, NC) was used for analyses.

Results

Sample

eFigure 1 illustrates flow of participants for these studies. From the 488 telephone-screened, 105 were enrolled and randomized [mean (SD) age, 40.5 (10.5); the majority were white/Caucasian participants (87.6%); and nearly sex balanced (females 58.1%)]. Table 1 displays the characteristics of the sample. Demographic characteristics were approximately matched between treatment arms, and no significant differences were found between groups for demographic and baseline characteristics presented in Table 1. The mean (SD) duration of PTSD was 215.3 (190.3) months, with trauma from various causes. Many participants had a lifetime history of positive suicidal ideation (86.8%) and/or behavior (30.9%). The optional supplemental dose was taken in 179/197 (90.9%) of blinded experimental sessions. The dropout rate was 7.6% (8/105), with six participants terminating early, but having completed at least one experimental session and follow-up assessment.

Primary outcome

The change in CAPS-IV total score (Fig. 1) from Baseline to after the second experimental session was significantly different [$t(95) = -4.25$, $P < 0.0001$] between control (0–40 mg) and active (75–125 mg) groups (Table 2). The active group had the greatest estimated mean (SE) drop in scores − 30.4 (3.20) compared to the control group − 10.5 (4.46). The between-group Cohen's *d* effect size was 0.8, indicating a large treatment effect. Study, age, PTSD duration, sex, race, and prior "ecstasy" use did not predict outcome in this model.

Secondary outcomes

According to CAPS-IV assessment at the endpoint 1–2 months post two experimental sessions (Table 2), more participants in the active group (54.2%) did not meet PTSD diagnostic criteria than the control group (22.6%). Depression symptom improvement on the BDI-II was greatest for the active dose group, estimated mean (SE) change active − 12.4 (1.84) versus control group − 6.5 (2.69), with the difference between groups trending toward significance [$t(61) = -1.97$, $P = 0.053$].

Depending on the study, after two blinded experimental sessions, most participants in the active dose group had one additional open-label (MDMA 100–125 mg, $n = 42$) or blinded session (MDMA 75–125 mg, $n = 9$). The estimated mean change (SE) from baseline to post third session on CAPS-IV for the active dose group was − 45.4 (3.61) with a significant further decline from second to third session [$t(95) = -12.58$, $P < 0.0001$]. The within-participant pre-test (baseline) to post-test Cohen's *d* effect size increased from 1.4 (post two sessions) to 1.9 (post three sessions). Due to the crossover, there is no between-group comparison for the post third session time point.

Safety and tolerability

Treatment-emergent adverse events (TEAEs) during the blinded treatment segment most commonly reported across all doses included events in the following MedDRA System Organ Classes (SOC): psychiatric disorders, gastrointestinal disorders, and general disorders (eTable 2). The most frequently reported psychiatric TEAEs (Table 3) were anxiety, depressed mood, irritability, and panic attack. On the day of blinded experimental sessions, reactions reported by ≥ 40% of participants in either group were anxiety, dizziness, fatigue, headache, jaw clenching/tight jaw, lack of appetite, and nausea. The majority of expected reactions were rated mild or moderate, and the frequency of reports decreased over the 7 days following an experimental session (eTables 5 and 6). No changes in neurocognitive function were detected (eTable 4).

There were no unexpected MDMA-related SAEs. Four SAEs were reported during the blinded treatment period, including one instance of suicidal ideation (30 mg) (Mithoefer et al. 2018); one SAE of exacerbation of ventricular extrasystoles was reported during an open-label session (125 mg) (Mithoefer et al. 2018) and one SAE of suicidal behavior prior to MDMA exposure in the first experimental session.

There was no suicidal behavior during the treatment period after dosing (eTable 3). At baseline, prior to any drug dosing, the active dose group (46%) had much higher rates of positive suicidal ideation than the control group (16.7%), but the lifetime reports (Table 1) were similar between groups. During the treatment phase, suicidal ideation transiently increased in some participants and was more common in the active MDMA group (eTable 3), although the causal relationship to the psychotherapeutic processing of traumatic memories or to MDMA itself, or to random group differences could not be determined.

Discussion

By pooling data across six phase 2 trials, we found significant symptom reductions in a large sample of participants with PTSD treated with active doses of MDMA combined with psychotherapy. The results informed the design of two phase 3 trials (one now ongoing the other to follow) that were approved through a Special Protocol Assessment by the FDA. The reproducible findings attained by various therapy teams in participants with PTSD arising from different types of traumatic experiences demonstrate the generalizability of this manualized drug-therapy approach and the applicability of the MAPS MDMA Therapy Training

Table 1 Demographics and baseline characteristics[a]

	Control ($n = 31$)	Active ($n = 74$)	Total ($n = 105$)
Age, mean (SD), years	40.4 (8.5)	40.5 (11.4)	40.5 (10.6)
Sex, *n* (%)			
Male	12 (38.7)	32 (43.2)	44 (41.9)
Female	19 (61.3)	42 (56.8)	61 (58.1)
Race, *n* (%)			
White/Caucasian	27 (87.1)	65 (87.8)	92 (87.6)
Latino/Hispanic	1 (3.2)	2 (2.7)	3 (2.9)
Native American	1 (3.2)	1 (1.4)	2 (1.9)
Middle Eastern	1 (3.2)	1 (1.4)	2 (1.9)
Other/biracial	1 (3.2)	5 (6.8)	6 (5.7)
BMI, mean (SD)	26.2 (6.1)	26.1 (5.4)	26.1 (5.6)
Duration of PTSD, mean (SD), months	197.9 (139.1)	222.6 (208.5)	215.3 (190.3)
Pre-study PTSD medications[b], *n* (%)			
Sertraline	10 (32.3)	25 (33.8)	35 (33.3)
Paroxetine	4 (12.9)	14 (18.9)	18 (17.1)
Pre-study therapy, *n* (%)			
CPT, IPT	0	4 (5.4)	4 (3.8)
Other CBT	24 (77.4)	34 (45.9)	68 (64.8)
EMDR	11 (35.5)	22 (39.7)	33 (31.4)
Group therapy	4 (12.9)	18 (24.3)	22 (21.0)
PE	3 (9.7)	5 (6.8)	8 (7.6)
Psychodynamic	9 (29.0)	14 (18.9)	23 (21.9)
Insight	6 (19.4)	15 (20.3)	21 (20.0)
Other	18 (58.1)	49 (66.2)	67 (63.8)
None	0	2 (2.7)	2 (1.9)
Prior ecstasy use, *n* (%)			
Yes	7 (22.6)	24 (32.4)	31 (29.5)
No	24 (77.4)	50 (67.6)	74 (70.5)
Lifetime C-SSRS[c], *n* (%)			
Positive ideation	14 (77.8)	45 (90.0)	59 (86.8)
Serious ideation	4 (22.2)	21 (42.0)	25 (36.8)
Positive behavior	6 (33.3)	15 (30.0)	21 (30.9)
CAPS-IV total score			
Baseline, mean (SD)	81.3 (15.9)	85.8 (19.3)	84.5 (18.4)
BDI-II total score[d]			
Baseline, mean (SD)	26.1 (10.6)	30.2 (11.6)	29.1 (11.4)

BMI, body mass index; CPT, cognitive processing therapy; IPT, interpersonal therapy; CBT, cognitive-behavioral therapy; EMDR, eye movement desensitization and reprocessing therapy; PE, prolonged exposure therapy; C-SSRS, Columbia–Suicide Severity Rating Scale; CAPS-IV, Clinician-Administered PTSD Scale; BDI-II, Beck Depression Inventory

[a] There were no significant group differences (χ^2 or independent *t* tests) for any variables presented in this table

[b] Sertraline and paroxetine are the only two FDA-approved medications for PTSD. Participants took many other medications for symptom management pre-study that are not presented here. Twelve participants took both sertraline and paroxetine

[c] Lifetime accounts for all suicidal ideation and behavior prior to study, according to participant recall and medical records. According to the C-SSRS scoring guide, scores of four or five on the suicidal ideation category are considered serious ideation, and scores of one or greater are considered positive behavior or ideation. Four phase 2 studies administered the C-SSRS (control group $n = 18$ and active MDMA group $n = 50$)

[d] For BDI-II, active group ($n = 50$) and control group ($n = 18$)

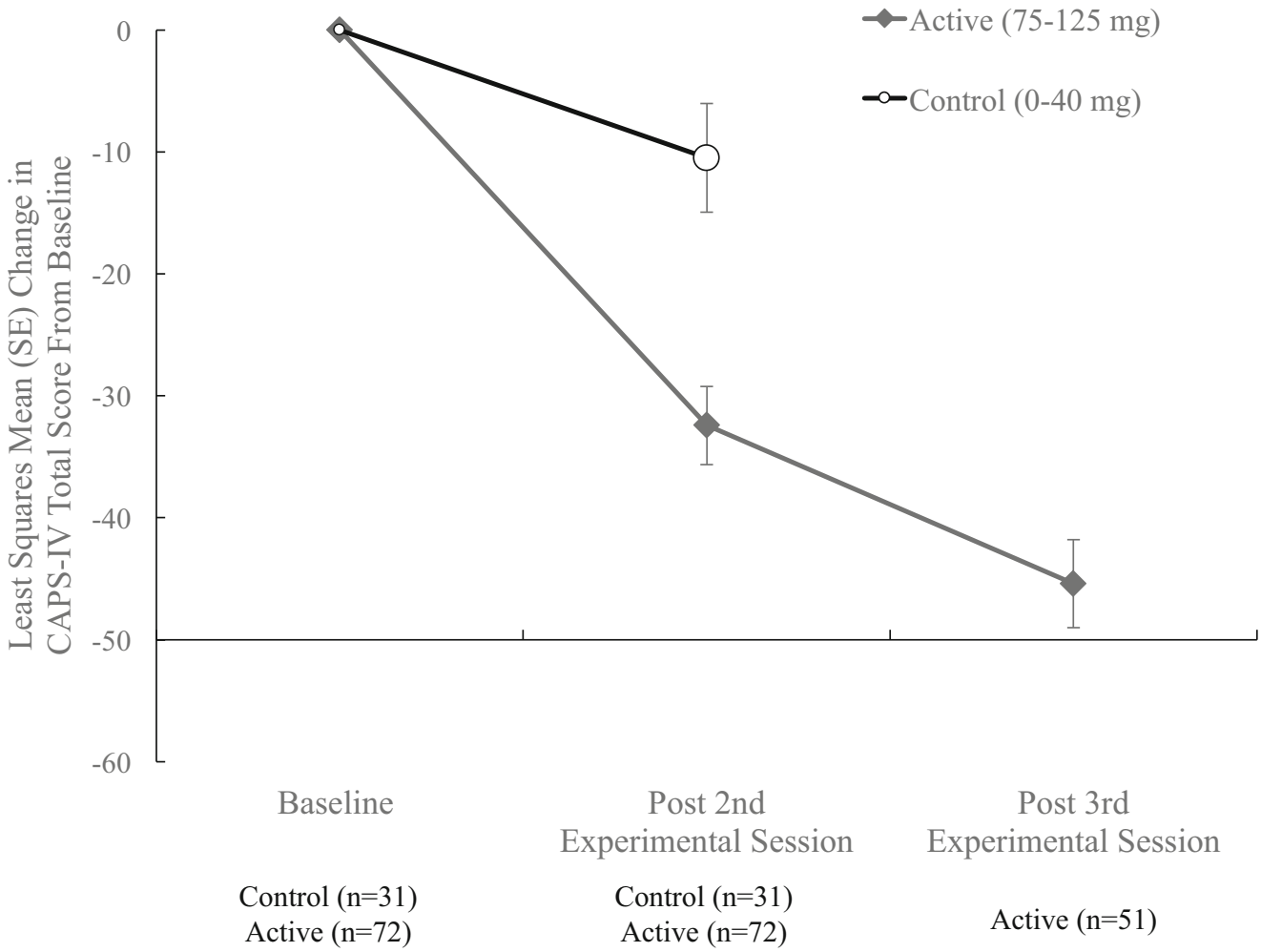

Figure 1 CAPS-IV total score least squared mean estimates at endpoints. The change in scores from baseline to post two experimental sessions were significantly different between MDMA and control groups (***$P < 0.0001$). After the third MDMA session, the active dose group showed further improvement compared to post two MDMA sessions (***$P < 0.0001$)

Program. Overall, the treatment was safe and efficacious for civilians and veterans/first responders with chronic PTSD who had previously failed to respond to pharmacotherapies and/or psychotherapy. More than half of the participants had previously undergone first-line trauma-focused psychotherapies, and all but two participants had received some type of psychotherapy prior to study enrollment. MDMA-assisted psychotherapy was effective for these individuals, suggesting a different mechanism of action for MDMA for reducing PTSD symptoms.

The data show that when using the "gold standard" measure of PTSD (CAPS-IV) as a primary outcome measure, with blinded raters, for participants with highly refractory PTSD (mean duration 215.3 months), there was a significant effect after two blinded active doses of MDMA adjunctive with psychotherapy versus psychotherapy with control doses. Notably, more participants in the active dose group (54.2%) no longer met PTSD diagnostic criteria compared to the control group (22.6%). The between-group effect size was large with Cohen's *d* equal to 0.8. The effect size was used in power calculations for phase 3 trials. Planned enrollment is 100 participants in each phase 3 trial, with an interim analysis and option for sample size adjustment after 60% of participants have completed the primary endpoint. In addition, depression symptoms trended toward greater improvement in participants receiving active MDMA compared with the control group.

After a third experimental session, symptoms on average improved further for the active dose group. The interpretation is limited because the third session was open label for most participants, and there was no control group for comparison due to the open-label crossover after two blinded sessions for most participants. However, it appears that while many people respond adequately after two MDMA sessions, an additional session leads to more participants reaching clinically significant symptom reductions and greater drops in CAPS-IV scores. For this reason, phase 3 trials will include three blinded experimental sessions to maximize response at the primary endpoint (2 months post third experimental session, i.e., 18 weeks post baseline).

Table 2 Outcome measures[a]

	Control ($n = 31$)	Active MDMA ($n = 72$)	Mean difference (control vs. active)
CAPS-IV total score			
Post 2 experimental sessions, LS (SE) change[b]	− 10.47 (4.46)	− 32.43 (3.20)	–
Difference (active − control)	–	–	− 21.95 (5.17)
P value	0.0208	< 0.0001	< 0.0001
Post 3 experimental sessions, LS (SE) change[b]	–	− 45.39 (3.61)[c]	–
P value	–	< 0.0001	–
Difference post 3 − post 2, LS (SE) change	–	− 12.97 (2.89)[c]	–
P value	–	< 0.0001	–
CAPS-IV PTSD diagnostic criteria met, *n* (%)			
Post 2 experimental sessions			
Yes	24 (77.4%)	33 (45.8%)	–
No	7 (22.6%)	39 (54.2%)	–
Post 3 experimental sessions[c]			
Yes	–	24 (47.1%)	
No	–	27 (52.9%)	–
BDI-II total score			
Post 2 experimental sessions, LS (SE) change[b]	− 6.46 (2.69)	− 12.44 (1.84)	–
Difference (active − control)	–	–	− 5.97 (3.03)
P value	0.019	< 0.0001	0.0534
Post 3 experimental sessions, LS (SE) change[b]	–	− 17.36 (1.89)	–
P value	–	< 0.0001	–
Difference post 3 − post 2, LS (SE) change	–	− 9.40 (5.66)	–
P value	–	0.1019	–

CAPS-IV, Clinician Administered PTSD Scale; BDI-II, Beck Depression Inventory-II; LS, least square mean estimates; SE, standard error

[a] All outcomes are based on intent-to-treat set

[b] Compared to baseline

[c] Active MDMA group ($n = 51$ for CAPS) post 3 experimental sessions, control group crossed over after 2 blinded sessions, except for MP2 study (data not included)

Phase 2 data showed that 75 mg MDMA produced significant improvement (Mithoefer et al. 2018), yet the sample was quite small ($n = 7$); therefore, we do not know what the optimal dose is, 75 mg, 100 mg, or 125 mg. There is individual variation in subjective effects of MDMA, and fixed-dose regimens do not account for differences in body weight. To gather more information about optimal dosing, phase 3 trials from 15 sites in the USA, Canada, and Israel will employ a flexible dose regimen. Participants will be randomized to receive equal-weight blinded capsules of inactive placebo or MDMA (80 mg) plus supplemental half-dose unless contraindicated in experimental session one, and then have the choice to escalate the dose to 120 mg with optional supplemental dose (or stay at 80 mg) in the next two sessions. An inactive placebo plus the same psychotherapy will be used as the control group, with the same option to escalate the dose. To minimize bias, a blinded independent rater (IR) pool will administer the primary outcome measure (CAPS-5) to participants across all sites based on availability of IRs. Consecutive assignments to the same IR will not be permitted. Independent raters will remain blinded to the number or timing of CAPS measurements in the study; therefore, we cannot reveal this information until the trials are complete.

The safety and tolerability of limited doses of MDMA in highly controlled therapeutic settings in a PTSD population was adequate, consistent with previous phase 1 studies. There was a dose effect for mean increase in vital signs during MDMA sessions (eTable 7), with values returning or trending toward baseline by the end of the 8-h session. Because vital sign increases did not reach clinically concerning ranges, the

Table 3 Treatment-emergent adverse events during the blinded treatment segment and expected reactions during two blinded MDMA sessions

	Control ($n = 31$)	Active MDMA ($n = 72$)	Total ($n = 103$)
Top reactions during experimental sessions, *n* (%)[a]			
Anxiety	15 (48.39)	52 (72.22)	67 (65.05)
Dizziness	6 (19.35)	29 (40.28)	35 (34.00)
Fatigue	18 (58.06)	35 (48.61)	53 (51.46)
Headache	22 (70.97)	38 (52.78)	60 (58.25)
Jaw clenching, tight jaw	6 (19.35)	46 (63.89)	52 (50.49)
Lack of appetite	7 (22.58)	35 (48.61)	42 (40.78)
Nausea	6 (19.35)	29 (40.28)	35 (33.98)
Psychiatric TEAEs, *n* (%)[b]			
Anxiety	3 (9.7)	17 (23.6)	20 (19.4)
Depressed mood	1 (3.2)	6 (8.3)	7 (6.8)
Irritability	0	3 (5.6)	3 (2.9)
Panic attack	0	3 (5.6)	3 (2.9)

TEAE, treatment-emergent adverse event

[a] Frequency of subjects who reported an expected, spontaneously reported reaction collected during blinded experimental sessions 1 and 2 (only reactions reported by ≥ 40% of participants in any group are displayed; see supplemental for full list of reactions)

[b] Frequency of subjects who self-reported psychiatric adverse events after first drug administration until the day before experimental session 3 (only AEs reported by three or more subjects in either group displayed)

frequency of required vital measurements will be reduced in phase 3 trials to baseline, pre-supplemental dose, and session end. Vital signs at the pre-supplemental dose reading will be taken into consideration before administering the additional half-dose. Neurocognitive measures will not be employed during phase 3 because phase 2 studies showed no evidence of cognitive impairment after two doses of MDMA (eTable 4).

MDMA at all doses tested was well tolerated, as demonstrated by the low rate of TEAEs and expected reactions. Most were mild to moderate, resolving as MDMA effects dissipated or during the week following (eTables 5 and 6). During experimental sessions, the active MDMA group had higher incidences of some reactions, including anxiety, dizziness, jaw clenching/tight jaw, lack of appetite, and nausea. Whether reactions are due to the pharmacological effects of MDMA or from augmented trauma processing catalyzed by MDMA effects cannot be determined from the data collected in these studies, but phase 1 studies in healthy individuals report similar reactions to MDMA. During the 7 days following experimental sessions, some reactions occurred more often in the active dose group for the first few days before declining by the end of the week. For this reason, the number of telephone contacts after an experimental session will be less frequent for phase 3 trials, which will require four telephone contacts over 7 days. In accordance with FDA guidance for all psychiatric drugs under development, the C-SSRS will be given at each in-person visit. In phase 2 trials, there were no related deaths or incidence of suicidal behavior after MDMA. The low dropout rate (7.6%) in MDMA trials compared to other PTSD treatments (approximately 17–36%) (Bradley et al. 2005; Marshall et al. 2001; Steenkamp et al. 2015) could be related to the propensity of MDMA to make trauma processing more tolerable with rapid symptom improvements in the days and weeks following. Participants in the placebo/control group had the opportunity to cross over to receive three open-label (100–125 mg) sessions of MDMA-assisted psychotherapy if they complete the blinded segment which likely motivated participants to complete treatment.

MDMA in the context of psychotherapy was found to have a low potential for abuse. There were no AEs or treatment discontinuation related to "ecstasy" seeking or craving, and no reports of use outside the study through the post third session endpoint. Indeed, many participates anecdotally reported that the experimental sessions were not particularly pleasurable experiences, but rather difficult therapeutic work delving into their traumatic memories. Overall, safety outcomes were favorable for use of MDMA in individuals with PTSD in a supportive environment with trained mental health professionals.

Limitations

There are limitations of these trials and the associated pooled data analyses. The sample was nearly gender balanced, but participants and therapists were predominantly White/Caucasian. Phase 3 studies will evaluate the generalizability to individuals from more diverse ethnic and cultural backgrounds. Across the six trials, there were variations in study design, such as differences in timing of outcome measures, doses tested, number of blinded experimental sessions, and number of participants in each dose group. Drawbacks of pooled data analyses are that multiple doses tested were combined into two groups—control group and active dose group—and that the third experimental session was blinded or open-label full-dose MDMA, depending on the study. Also, there was no control group for a between-group comparison of the post third session; therefore, response after three sessions was limited to a within-subject analysis. Due to small sample sizes, reliability of effect size estimates from individual studies is unknown. Blinding of treatment assignment for psychoactive substances is a recognized challenge. Both psychological and vital sign changes during experimental sessions can be clues to the group assignment. To reduce bias, blinded independent raters who were not present during therapy sessions administered the CAPS-IV. However, participants and therapists often, but not always, accurately guessed dose assignment (Mithoefer et al. 2011, 2018; Oehen et al. 2013; Ot'alora et al. 2018)—a recognized limitation in clinical trials of all

drugs with perceivable effects and in all psychotherapy studies where there is no possibility of effective blinding.

Conclusions

Based on the promising safety and efficacy results from these six phase 2 trials, we have designed multi-site, placebo-controlled phase 3 trials that started in late 2018 to evaluate MDMA-assisted psychotherapy in approximately 200 participants with PTSD. Limitations discussed here will be addressed, and if findings are significant and no new safety concerns arise, MDMA could become an FDA-approved treatment for PTSD in the context of psychotherapy by 2021.

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Author contributions S.H. is responsible for integrity of the data and accuracy of data analysis.

Study concept and design: M.C.M., A.M., L.J., A.E., B.Y.-K., R.D., M.W.

Acquisition, analysis, or interpretation of data: all authors.

Drafting of the manuscript: A.A.F., L.J., M.C.M., M.W., Z.W.

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Role of the funder/sponsor MAPS and MAPS PBC assisted with study design; monitoring of study data; analysis, management, and interpretation of data; preparation, review, and approval of manuscript; and decision to submit the manuscript for publication. The funder had no role in the collection of data or conduct of the study.

Compliance with ethical standards

Conflict of interest M.C.M. received salary support from MAPS PBC as a clinical investigator and clinical trial medical monitor as well as for training and supervision of research psychotherapists.

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REVIEW
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Breakthrough for Trauma Treatment: Safety and Efficacy of MDMA-Assisted Psychotherapy Compared to Paroxetine and Sertraline

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Unsuccessfully treated posttraumatic stress disorder (PTSD) is a serious and life-threatening disorder. Two medications, paroxetine hydrochloride and sertraline hydrochloride, are approved treatments for PTSD by the Food and Drug Administration (FDA). Analyses of pharmacotherapies for PTSD found only small to moderate effects when compared with placebo. The Multidisciplinary Association for Psychedelic Studies (MAPS) obtained Breakthrough Therapy Designation (BTD) from the FDA for 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for treatment of PTSD on the basis of pooled analyses showing a large effect size for this treatment. This review covers data supporting BTD. In this treatment, MDMA is administered with psychotherapy in up to three monthly 8-h sessions. Participants are prepared for these sessions beforehand, and process material arising from the sessions in follow-up integrative psychotherapy sessions. Comparing data used for the approval of paroxetine and sertraline and pooled data from Phase 2 studies, MAPS demonstrated that MDMA-assisted psychotherapy constitutes a substantial improvement over available pharmacotherapies in terms of safety and efficacy. Studies of MDMA-assisted psychotherapy had lower dropout rates compared to sertraline and paroxetine trials. As MDMA is only administered under direct observation during a limited number of sessions, there is little chance of diversion, accidental or intentional overdose, or withdrawal symptoms upon discontinuation. BTD status has expedited the development of MAPS phase 3 trials occurring worldwide, leading up to a planned submission seeking FDA approval in 2021.

Clinical Trial Registration: www.ClinicalTrials.gov, identifiers NCT00090064, NCT00353938, NCT01958593, NCT01211405, NCT01689740, NCT01793610.

Keywords: methylenedioxymethamphetamine, posttraumatic stress disorder, breakthrough therapy, sertraline, paroxetine, anxiety

INTRODUCTION

Breakthrough therapy designation (BTD) is one of the Food and Drug Administration's (FDA) expedited drug development pathways. To be eligible for BTD, a sponsor must demonstrate that the investigational product is intended to treat a serious and life-threatening condition, with preliminary evidence supporting a substantial advantage at a clinically significant endpoint over existing drugs (1). On August 16, 2017, the FDA granted breakthrough therapy designation for MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder (PTSD). This application was among the 45% of applications granted BTD status in 2017 (2). The aim of this review is to summarize the data and rationale presented in the application that led FDA to grant this designation.

PTSD is considered a serious and life-threatening disorder and is associated with increased mortality, cardio-metabolic morbidity, and suicide risk. PTSD negatively impacts a person's daily life, often resulting in fractured relationships, depression, decreased daily functioning, diminished cognitive and psychosocial functioning, substance abuse, and high-cost healthcare utilization ($34.9 billion in inflation-adjusted charges for hospitalizations (2002–2011) (3). Approximately 7% of the U.S. population, and 11.2–17.1% of veterans (4), will have PTSD sometime in their life (5).

Only two drugs, the selective serotonin reuptake inhibitors (SSRIs) sertraline hydrochloride (Zoloft) and paroxetine hydrochloride (Paxil), are approved oral medications for PTSD (6–8). These medications and trauma-focused psychotherapies (e.g., eye movement desensitization, cognitive processing therapy, prolonged exposure) are recommended as first-line treatments for PTSD (9–12). In a meta-analysis evaluating psychotherapy versus pharmacotherapy, trauma-focused psychotherapies resulted in greater and longer lasting improvements than medications (12). Meta-analyses and network meta-analyses found paroxetine, but not sertraline, performed better than placebo (13, 14). Hoskins and colleagues reported that SSRIs had a small effect size with respect to PTSD symptom reduction. When compared to a control group, SSRIs either had insignificant effects or small/moderate effects, while trauma-focused therapies varied from small to large effects (12). The average dropout rate for the 55 studies included in the meta-analysis was 29% (0–79%) demonstrating that many individuals fail to tolerate or respond to available treatments (12), including trauma-focused psychotherapies, where the dropout can range from 28 to 68% (15, 16). A network meta-analysis reported that dropout rate for paroxetine and sertraline was greater than placebo (14).

The Multidisciplinary Association for Psychedelic Studies (MAPS) holds an Investigational New Drug Application (IND) for MDMA as an adjunct to psychotherapy for treatment of PTSD. MAPS has sponsored six phase 2 trials of MDMA-assisted psychotherapy for PTSD that lasted from April 2004 to March 2017. The safety and efficacy results from these trials were submitted to the FDA, along with a summary of the sertraline and paroxetine data that supported the New Drug Application (NDA) for approval of these drugs for the indication of PTSD. Sertraline and paroxetine summary data was extracted from documents found in the FDA drug database, including the Review and Evaluation of Clinical Data and the drug labels (17–20).

Here, we present the evidence included within the breakthrough therapy application showing that MDMA-assisted psychotherapy was superior in phase 2 trials in terms of safety and efficacy compared to the two approved SSRIs for treatment of PTSD. The control groups in the MDMA trials also received intensive psychotherapy (approximately 30 h), while SSRIs pivotal trials used a placebo without any type of therapy for comparison. Since the FDA does not regulate psychotherapy, the BT application did not compare MDMA-assisted psychotherapy to trauma-focused therapies. However, since trauma-focused therapies have evidence for the greatest effectiveness in reducing PTSD symptoms, we have included an additional section in this review comparing MDMA-assisted-psychotherapy with first-line psychological therapies.

EFFICACY AND DURABILITY OF RESPONSE: MDMA VS. SSRIS

MDMA-Assisted Psychotherapy

MDMA is a ring-substituted phenethylamine that is classified as an entactogen in the Merck Index (21) due to its properties that can promote empathy and compassion for self and others. MDMA stimulates release of serotonin, norepinephrine and dopamine, and may act directly on some adrenergic, cholinergic, and serotonergic receptors (22). MDMA elevates levels of the neurohormone oxytocin, an effect likely mediated through direct or indirect action on 5HT1A, 5HT2A, and 5HT4 receptors (23–25), as well as elevating levels of prolactin, arginine vasopressin (AVP), adrenocorticotrophic hormone (ACTH), and cortisol (26–29). MDMA possesses a unique pharmacodynamic profile in humans that includes increased emotional empathy, an increase in feelings of interpersonal closeness, greater prosocial behavior, and an increased ability to tolerate distressing memories, greater reward from pleasant memories, and less distress in response to social exclusion (30–34). Imaging studies found that MDMA reduced activity in brain areas associated with anxiety, including the amygdala, and increased activity in prefrontal cortex (35–37). Hypotheses for MDMA's therapeutic action include enhanced fear extinction, memory reconsolidation, enhanced therapeutic alliance, widening a window of tolerance for distressing thoughts or experiences, and re-opening or enhancing a critical period for experiencing social reward (25, 38, 39). It is likely through these effects that MDMA augments and enhances effectiveness of psychotherapy.

Investigators have developed standardized psychotherapeutic methods for combining MDMA and psychotherapy that include up to 3 sessions with MDMA and up to 12 non-drug sessions. During preparatory sessions participants meet with the two co-therapists, usually one male and one female, when they discuss their goals, and concerns, and learn what to expect during the MDMA-assisted session. The psychotherapy during MDMA-assisted sessions is relatively non-directive, supporting the participants spontaneous experience, and designed to

facilitate processing of challenging emotions in a safe and controlled setting (40–44). Participants may use eye shades, and may listen to a program of music designed to support the therapy. Periods of inner focus alternate with periods of talking to the therapists. Vital signs are assessed periodically. Material arising during MDMA-assisted psychotherapy sessions is integrated in subsequent psychotherapy visits. Subsequently, participants are encouraged to make time to explore and express their unfolding experience using journaling or artwork. Participants in Phase 2 studies were contacted for 7 days after each experimental session. More information concerning MDMA-assisted psychotherapy can be found in publications and in the MDMA Treatment Manual (42). Studies with a long term follow up demonstrate durable improvement in PTSD (41, 43–45), social anxiety in autistic adults (46), and anxiety associated with facing a life threatening illness (22, 38).

Phase 2 Trials of MDMA-Assisted Psychotherapy for PTSD Treatment

The six Phase 2 studies of MDMA-assisted psychotherapy that supported the breakthrough application followed a randomized, double-blind, placebo-controlled design with the Clinician-Administered PTSD Scale for DSM-IV (CAPS-IV) as the primary efficacy measure (41, 44, 45, 47, 48). The CAPS-IV is an established measure of PTSD symptoms (49, 50). To enroll, participants were required to have a CAPS-IV total severity score of 50 or greater and to have failed to respond to or tolerate at least one course of treatment. The average duration of PTSD was 17.9 years. The basic study design for the six studies included three preparatory psychotherapy sessions, followed by 2–3 blinded, 8-h experimental psychotherapy sessions with MDMA (75–125 mg) or comparator/placebo (0–40 mg MDMA), and three 90-min non-drug integrative psychotherapy visits following each experimental session. Experimental sessions were scheduled approximately a month apart. Independent Raters (not present during treatment, blinded to group assignment) administered CAPS-IV at baseline, primary endpoint (3–8 weeks after two blinded sessions, or after three sessions in one study), and secondary endpoints (time points during the open-label crossover and at the 12-month follow-up).

Data was pooled across the six phase 2 studies (**Table 1**). Results showed that the active dose group (MDMA 75–125 mg, n = 72) was statistically superior to the control group (0–40 mg, n = 31) at the primary endpoint (independent samples t-test, $p < 0.001$), with average (SD) drop in CAPS-IV total scores −37.8 (29.29) for the active group and −11.6 (17.93) for the control group. There was large between-group Cohen's *d* effect size (0.9).

Prior to enrollment in MAPS-sponsored Phase 2 trials, 17 and 35 subjects (of n = 105) had previously taken paroxetine and sertraline, respectively (**Table 2**). Twelve participants had tried both SSRIs. These individuals did not reach adequate symptom reduction or failed to tolerate the SSRIs. From this subset, 20/38 (52.6%) subjects that received active doses of MDMA (75–125 mg) no longer met criteria for PTSD at the primary endpoint. The average drop in CAPS-IV total scores was −40.1 (25.66) for participants who had previously taken paroxetine and −35.04 (27.5) in participants who had previously taken sertraline (**Table 2**). The other 14 subjects were randomized to the control group. The high response rate and large drops in CAPS-IV total score in this subset suggests that MDMA therapy may be able to effectively treat PTSD in individuals who do not adequately respond to SSRIs.

TABLE 1 | Pooled CAPS-IV data from six phase 2 MAPS-sponsored studies of MDMA-assisted psychotherapy.

	Active group (MDMA 75–125 mg) N = 72	Control group (MDMA 0–40 mg) N = 31
Change in CAPS-IV total scores [a], mean (SD)	−37.8 (29.29)	−11.6 (17.93)
Cohen's *d* effect size[b]	1.5	0.6
Dropouts, n (%)[c]	5 of 74 (6.8%)	3 of 31 (9.7%)

[a]*Change in CAPS-IV scores from baseline to the primary endpoint (1–2 months post 2–3 MDMA sessions).*
[b]*Within-group Cohen's d effect size calculated by dividing the change from baseline to primary endpoint by the standard deviation.*
[c]*For the active group, 3 terminated early but completed an endpoint assessment and 2 terminated early with no endpoint assessments. For the control group, 3 terminated early but completed an endpoint assessment.*

TABLE 2 | Mean change from baseline to the primary endpoint in CAPS-IV total scores in MAPS-sponsored phase 2 subjects who had previously taken sertraline, paroxetine, or both.

	Paroxetine n = 17	Sertraline n = 35	Paroxetine/ sertraline n = 12
Control group, mean (SD) (MDMA 0–40 mg)	−21.0 (24.01) n = 4	−15.9 (16.87) n = 10	−30.3 (18.50) n = 3
Active group (MDMA 75–125 mg)	−40.1 (25.66) n = 13	−35.04 (27.5) n = 25	−38.2 (29.90) n = 9

Sertraline Phase 3 Trials for PTSD

Sertraline was investigated by Pfizer for treatment of PTSD in four studies of similar design with a 12-week flexible dose (50, 100, 150, and 200 mg with 25 mg starting dose for titration) (17, 20). Subjects who met DSM-III-R criteria with a CAPS-2 total score of 50 or greater were enrolled. Patients had a mean duration of PTSD for 12 years and 44% of patients also had a depressive disorder. Two of the four studies failed to find a significant difference between the sertraline and placebo treated groups on any of the primary efficacy outcomes. One study (640, n = 208) reported efficacy on CAPS-2 total score at week 12 [last observation carried forward (LOCF) method, $p = 0.043$] but not week 12 [observed case (OC)] or any earlier weeks. Placebo-subtracted effect size was 0.31, with a 6.8 point mean difference between groups in CAPS-2 total score (LOCF). The other study (671, n = 183) detected efficacy (OC) of sertraline at weeks 2 ($p = 0.041$), 4 ($p = 0.0002$), 6 ($p = 0.011$), 8 ($p = 0.006$),

10 (p = 0.04), and 12 (p = 0.016) on CAPS-2 but only in females which was influenced by mood improvement.

A combined analysis of the two positive studies found a significant difference between sertraline and placebo groups only in women but not in men. Results suggest much of the effect on PTSD scales correlated with improvement in the HAM-D, therefore it is unclear whether sertraline treats PTSD or comorbid depression, an indication the drug was already approved for. The report stated that there was insufficient evidence to support any efficacy claim beyond 3 weeks of treatment. However, a longer-term study that randomized responders (n = 96) in a 24-week open-label continuation trial of sertraline (50–200 mg/day), or switched to placebo for 28 weeks, found significantly reduced relapse rates for the sertraline group, in both males and females.

Paroxetine Phase 3 Trials for PTSD

Paroxetine (20–50 mg/day) demonstrated superiority over placebo on change from baseline for the CAPS-2 total score in two multicenter, placebo-controlled studies in adults who met DSM-IV criteria for PTSD. The trials were sponsored by GlaxoSmithKline (18, 51). In these studies, 858 patients had PTSD symptoms with duration on average of 13 years. Major depressive disorder was present in 41% of patients and non-PTSD anxiety disorder was reported for 40% of patients. Primary outcomes were change from baseline to endpoint on CAPS-2 total score and the proportion of responders assessed by the Clinical Global Impression-Global Improvement Scale (CGI-I), a 3-item observer-rated scale.

In Study 1 (20 and 40 mg) and Study 2 (20 and 50 mg), paroxetine was significantly superior to placebo on both outcome measures. In Study 1 (n = 551), paroxetine was better than placebo (p < 0.001) at 4, 8, and 12-week time points for the LOCF and OC analyses. 71% of 40 mg paroxetine and 76% of 20 mg paroxetine treated patients met response criteria on CGI-I compared to 48% of placebo (p < 0.001). The difference between paroxetine and placebo groups on CAPS-2 total score was approximately 14 units for LOCF and OC analyses for both dose groups. In Study 2 (n = 307), paroxetine was better than placebo (p < 0.001) at 12-week time point for the LOCF and OC analyses. 76% of paroxetine treated patients met response criteria on CGI-I compared to 50% of placebo (p < 0.001). The difference between paroxetine and placebo groups on CAPS-2 total score was approximately 11 units for LOCF and 14 units for OC.

A third study with flexible doses (20–50 mg) found paroxetine to be significantly better than placebo on CAPS-2 total score, but not on CGI-I responders (defined as patients having a score of 1 "very much improved" or 2 "much improved"). In Study 3 (n = 322), CAPS-2 total score was statically superior in paroxetine group compared to placebo for LOCF (p = 0.047) but not OC analysis (p = 0.071) at the 12-week time point. On the CGI-I, 60% of paroxetine treated subjects met response criteria compared to 52% of placebo (not statistically significant). The difference between paroxetine and placebo groups on CAPS-2 total score was approximately 6 units for LOCF and OC analysis. Analyses did not detect any differences in gender on treatment outcomes.

The difference in CAPS-2 total scores between paroxetine and placebo in mean change from baseline at 12 weeks was roughly 6-14 units across the three studies. According to the drug label, the efficacy of paroxetine to treat PTSD beyond 12 weeks had not been investigated in controlled clinical trials, yet PTSD is a chronic condition.

Comparison: SSRIs vs. MDMA

Primary efficacy evaluation of six MAPS-sponsored phase 2 trials on change from Baseline to Primary Endpoint in CAPS-IV Total Severity indicated a significant effect of MDMA over the comparator group (p < 0.001), with a large between-group effect size (0.9 Cohen's *d* effect size) that was approximately double that of paroxetine (0.45–0.56) and triple that of sertraline (0.31–0.37). In comparison of mean change in CAPS total scores, placebo subtracted scores for sertraline ranged from 6.8–9.8 units, for paroxetine 6–14 units, and for MDMA 26.2 units (**Table 3**). The fact that the control group in MDMA studies received the same intensive psychotherapy as the active dose group adds to the clinical significance of these differences. Results from MAPS-sponsored MP-1 study detected significant (p = 0.013) difference between MDMA (125 mg) and placebo groups on CAPS-IV total scores 3–5 days after the first experimental session, demonstrating a rapid clinical response after a single MDMA dose. SSRIs require at least 2 weeks of daily dosing with dose titrations to produce any detectable PTSD symptom improvements, and one pivotal

TABLE 3 | Comparison of sertraline, paroxetine, and MDMA mean CAPS reduction LOCF, intent-to-treat.

	Sertraline		Paroxetine		MDMA	
	CAPS-2 (sertraline–placebo)[a]	Dropout %	CAPS-2 (paroxetine–placebo)[a]	Dropout %	CAPS-IV (MDMA–control)[b]	Dropout %
Study 1	–6.8 (effect size 0.31)	29.3%	–14 (effect size 0.56)	35.5%	–26.2 (effect size 0.9)	7.6%
Study 2	–9.8 (effect size 0.37)	28.4%	–11 (effect size 0.45)	39.0%	—	
Study 3	—		–6 (effect size 0.09)	33.0%	—	

[a]*Effect sizes were not reported in FDA statistical package for paroxetine. Placebo subtracted effect. Size were determined from CAPS scores by calculating the change from baseline divided by the standard deviation.*

[b]*Primary endpoint was 1–2 months after 2–3 blinded experimental sessions.*

study of sertraline and one of paroxetine did not find significant improvement until after 12 weeks of daily drug administration. The beneficial effects of MDMA-assisted psychotherapy have been shown to last for at least 12 months in many participants (67.8% of n = 90 did not meet diagnostic criteria), while paroxetine (12 weeks) and sertraline (3 weeks) drug labels specify that long-term efficacy was not assessed. Sertraline was only shown to statistically significant in women and not men, while MDMA has been effective for both males and females with no difference in response measured

Sertraline and paroxetine demonstrated superiority on the CAPS-2 over placebo in two 12-week pivotal trials which led to a new marketing label for the indication of PTSD. Both had small to medium placebo-subtracted effect sizes (0.31–0.37 and 0.45–0.56, respectively) and require daily dosing for 12 weeks.

COMPLIANCE AND SAFETY: MDMA VS. SSRIS

The dropout rate in active (75–125 mg blinded) MDMA-treated subjects in MAPS-sponsored Phase 2 trials was 6.8% (5 of 74, with 2 excluded for missing outcome data and 3 excluded for early termination, with outcome data), considerably less than SSRI trials where dropout rates were 11.7% in paroxetine-treated and 28% in sertraline-treated subjects, indicating that MDMA is better tolerated by a PTSD population than the two SSRIs. Reduced drop-out rates in MAPS' Phase 2 studies may result from a strong therapeutic alliance, and commitment to the course of psychotherapy, as well as the therapeutic effects of MDMA. On the other hand, dropout rates (3 of 31, 9.7%) were also low for the control group which could reflect some benefit from the psychotherapy alone, or increased motivation to remain in the study to receive active MDMA during the open-label crossover segment.

In paroxetine trials, the most common adverse events (5% or greater and at least 2× that of placebo) in the PTSD population were: asthenia, sweating, nausea, dry mouth, diarrhea, decreased appetite, somnolence, libido decreased, abnormal ejaculation, female genital disorders, and impotence. Reported by 19% of subjects, nausea was the most frequently experienced treatment-emergent adverse event. For sertraline, the most common effects were nausea, headache, insomnia, diarrhea, dry mouth, ejaculation failure, somnolence, dizziness, and fatigue.

Administering MDMA in single doses spaced a month apart in a controlled setting has several inherent benefits over chronic daily dosing of paroxetine or sertraline. Firstly, compliance is not an issue in studies of MDMA, because all dosing occurs in a clinic under supervision, whereas SSRIs rely on patients self-administering daily doses which can be a challenge due to cognitive and behavioral impairments that can accompany PTSD (52).

Secondly, fewer side effects are reported after MDMA due to the limited number of administrations. Phase 2 safety data showed that reactions were reported most frequently on the day of MDMA administration and typically diminished in the few days following. The most commonly reported reactions on the day of the experimental session were anxiety, tight jaw/jaw clenching, lack of appetite, headache, and fatigue (48). On the day of blinded experimental sessions, reactions reported by the active MDMA group by at least 2x of the frequency of the control group were diarrhea, difficulty concentrating, dizziness, heavy legs, impaired gait/balance, jaw clenching/tight jaw, lack of appetite, nausea, nystagmus, paresthesia, perspiration, sensitivity to cold, thirst, and weakness. These findings are in line with clinical trials in healthy controls (53, 54). On the other hand, patients taking paroxetine and sertraline experience more prolonged adverse reactions due to steady state drug plasma levels across the 12-week treatment period.

Discontinuation of paroxetine and sertraline may be accompanied by adverse effects (55), likely caused by neuroadaptations of decreased levels of serotonin transporters in neuronal membranes after use of SSRIs (56). For discontinuation of sertraline and paroxetine gradual tapering is recommended, and patients should be monitored for discontinuation emergent symptoms, which can be very troubling. Adverse events during discontinuation (incidence of 2% or greater for paroxetine and at least 2x that of placebo) were abnormal dreams, paresthesia, and dizziness, and for sertraline, they were nausea, insomnia, and diarrhea (18, 20). Post-marketing surveillance identified a number of additional discontinuation emergent negative effects, including sensory disturbances, agitation, anxiety, nausea, and sweating; however causal relationship to drug hasn't been confirmed.

Single doses of MDMA have not produced discontinuation symptoms. Some adverse reactions are reported during the 7 days following an MDMA dose, including anxiety, dizziness, depressed mood, fatigue, headache, jaw clenching or tightness, lack of appetite, nausea, and panic attack (48). By Day 5, the only reactions reported in over 20% of active dose participants were fatigue and anxiety. Both were reported by nearly equal numbers of active and control dose participants. Symptoms were mild to moderate in severity, and nearly all resolved within 7 days of dosing. Eight participants in the active dose group and three in the control group, reported a reaction on the seventh day of follow-up (not seven consecutive days of experiencing the reaction) that was therefore recorded as an adverse event (AE). Reactions fitting AE criteria and reported by more than two participants were anxiety and low mood, occurring in both active and control groups. Both are prominent symptoms of PTSD. Only three participants had the same reaction on day of experimental session and 7 days following the session, which included anxiety, low mood, and muscle tension.

Estimating risk of long-term deleterious effects of discrete doses of MDMA in a controlled setting compared to retrospective studies in people reporting ecstasy use is inappropriate for several reasons. Ecstasy can contain an unknown quantity of MDMA and adulterants, or no MDMA at all, and most people ingesting MDMA are polydrug users. Most studies are retrospective, with only a single prospective study reported detecting signs of a specific impairment in verbal memory in a sample of people reporting nonmedical use, without detecting any functional or structural changes in the brain (57, 58). Systematic reviews of the literature found that most research enrolls people whose lifetime

use far exceeds the average (59–61). In contrast, cognitive function in three trials of MDMA-assisted psychotherapy failed to find impairment after any dose of MDMA (48). When asked about 'ecstasy' use at 12-month follow-up after participation in a Phase 2 trial, eight participants, six of whom had taken ecstasy prior to enrollment, reported having used it one to three times. This indicates that MDMA given in the context of psychotherapy does not have high abuse liability (41, 43, 44, 47, 62).

An additional risk of SSRIs is that they are contraindicated with MAOIs and some other drugs due to inhibition of P450 enzymes. Since these drugs are take-home medications, patients are at risk of accidentally consuming a contraindicated medication that could have serious adverse effects, including death. Accidental and intentional overdoses have been reported with both SSRIs (63). Since clinicians collect concomitant medication information at each session before administering MDMA, the risk for accidental use of a contraindicated medication is far reduced, and risk of overdose is eliminated by dispensing only the recommended dosage by a prescribing physician. Both SSRI drug labels state that alcohol is not recommended, but given that a significant number of people with PTSD also have comorbid alcohol use disorders, refraining from alcohol may be particularly problematic for this population and lead to negative effects (64, 65).

MDMA-assisted psychotherapy received BTD based on its use in treating PTSD, a serious and life-threatening condition, and on the basis of phase 2 clinical data that MDMA produced substantial clinical improvement and greater compliance than the two approved drugs for PTSD, paroxetine and sertraline. Data from Phase 2 provides evidence that PTSD, independent of cause, is treatable with 2 to 3 sessions of MDMA-assisted psychotherapy, and offers a larger treatment effect, increased compliance and lower risk of dropout, reduced possibility of drug interactions compared to paroxetine and sertraline. There have been no deaths related to MDMA in controlled Phase 1 and 2 studies, and if it is approved for clinical use, MDMA will be administered directly to patients, and only in licensed MDMA clinics under controlled conditions similar to those in clinical research. The single-dose regimen of MDMA produces fewer, self-limiting, transient side effects and greater compliance compared to daily dosing of paroxetine and sertraline.

COMPARISON OF MDMA-ASSISTED PSYCHOTHERAPY VS. TRAUMA-FOCUSED THERAPIES

In meta-analyses comparing efficacy of PTSD treatments investigated in randomized controlled trials, trauma-focused psychotherapies generally result in greater and more sustained response than pharmacotherapies and other psychological therapies (12, 66). Lee et al. report comparative effect sizes from meta-analyses of randomized trials that included a control condition, with controls for psychotherapy trials including supportive psychotherapy, biofeedback, and relaxation training, and excluding those with waitlist and treatment-as-usual controls. Compared to control, after 14–27 weeks of trauma-focused therapies the effect size was −0.96. For all medications, which included SSRIs, SNRIs, antiepileptics, antipsychotics, the effect size was −0.44. The magnitude of effect (0.9) of MDMA-assisted psychotherapy is in the range of first-line trauma-focused therapies. MDMA was compared to psychotherapy alone, or low dose MDMA plus psychotherapy, as the control condition and Phase 2 studies enrolled only participants who had previously tried and failed to respond to or tolerate available treatments.

Beyond the quantifiable change of PTSD symptoms, the degree to which MDMA supports the unfolding of a healing experience through neurochemical changes should be considered. Biochemically inducing a mental state more receptive to engaging in deep therapeutic processing could help to speed up symptom improvement or improve treatment outcomes for those resistant to other therapies. There is some evidence from nonclinical experiments that MDMA may increase neuroplasticity through BDNF-dependent mechanism (67), and otherwise alter brain activity in key networks for emotional-memory processing (30). Psychologically, MDMA may ease the challenge of recalling traumatic memories and feeling deeply into the associated emotions. Posttraumatic growth measured by the Posttraumatic Growth Inventory (PTGI), and personality shifts measured by the NEO Personality Profile have been observed after MDMA-assisted psychotherapy (43, 68). In addition, the importance of patient choice regarding therapy for PTSD has been pointed out, and MDMA-assisted psychotherapy may offer advantages in this area if it makes processing trauma less arduous (69).

Another recent meta-analysis paper, found no significant differences in benefits of pharmacological, psychotherapeutic, or the combination at the end of treatment, except at the last available endpoint during long-term follow-up, at which point psychotherapeutic treatments were significantly better than medications. In this analysis, the combined treatments, which included one MDMA-assisted psychotherapy trial, were slightly but not significantly more beneficial than psychotherapeutic treatments alone (66). Data from the other five phase 2 MDMA trials were not included, and the outcome from the MDMA trial was analyzed along with other medication-therapy combinations (e.g., SSRIs and CBT). Until MDMA-assisted psychotherapy is compared to trauma-focused therapies in a randomized trial, it is uncertain whether either approach is superior in terms of efficacy or tolerance. Though it may potentially have greater risks and increased likelihood of mild to moderate adverse events compared with non-drug therapies, MDMA has thus far demonstrated a favorable safety profile with limited administrations in clinical settings. Patient experience of each therapy, time to respond, and durability of response should be evaluated. Future research could also explore whether MDMA combined with existing manualized trauma-focused therapies potentiates PTSD symptom reduction.

STATUS OF MDMA DRUG DEVELOPMENT WITH BREAKTHROUGH DESIGNATION

BTD is intended to expedite the development and approval of promising treatments by allowing for more frequent interactions

with the FDA, rolling review of documents, and the possibility for priority review (6 months rather than the normal 10-month review period) (1). BTD also receives an organizational commitment from the FDA with more guidance and involvement of FDA senior managers for efficient drug development.

After receiving BTD for this program, MAPS and the FDA also reached agreement under the Special Protocol Assessment (SPA) process for the design of two multi-site Phase 3 trials (MAPP1 and MAPP2) of MDMA-assisted psychotherapy for patients with at least severe PTSD. These two pivotal Phase 3 trials will enroll approximately 200-300 participants at sites in the USA, Canada, and Israel.

The pivotal Phase 3 trial started in November 2018. If Phase 3 trials produce significant confirmatory results and satisfactory safety profile, an application for marketing approval of MDMA-assisted psychotherapy for PTSD will be filed with the FDA. Filing of a New Drug Application is projected for 2021, with anticipated approval in 2022.

CONCLUSION

It is anticipated that MDMA, with its unique pharmacological mechanisms combined with psychotherapy, has advantages over existing medications used as first-line PTSD treatments in terms of safety and side effect profiles, efficacy, and length of remission. PTSD is a chronic condition that afflicts a substantial number of individuals who do not adequately respond to available therapies and are at increased risk of suicide, other mental health conditions, cardiovascular disease, and cognitive impairment. Findings from both nonclinical and clinical studies support a novel mechanism by which MDMA amplifies the therapeutic effects of psychotherapy by a dynamic interaction of brain regions, and affiliated neurochemicals therein, known to be involved in fear extinction learning, memory reconsolidation, emotional processing, and cognition (30, 32, 39, 48, 70). With many apparent advantages over existing medications, including efficacy, tolerability, and duration of therapeutic effects, MDMA-assisted psychotherapy has the potential to favorably impact the lives of thousands who suffer from PTSD world-wide.

AUTHOR CONTRIBUTIONS

Concept and review design: LJ, AF, AE, BY-K, RD, and MM. Acquisition, analysis, or interpretation of data: LJ, AF, AE, BY-K, RD, and MM. Drafting of the manuscript: LJ, AF, AE, BY-K, RD, and MM. Critical revision of the manuscript for important intellectual content: LJ, AF, AE, BY-K, RD, and MM. Obtained funding: RD.

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