

Utah Mental Illness Psychotherapy Drug Task Force Report to the Utah Legislature

October 2022

Prepared by

Utah Mental Illness Psychotherapy Drug Task Force

Table of Contents

[List of Abbreviations](#)

[Executive Summary](#)

[Introduction](#)

[Task force history](#)

[Task force duties](#)

[Task force structure](#)

[Task force meetings](#)

[Task force workgroups](#)

[Evidence review process](#)

[Highlights from evidence review](#)

[Indications and prescribing practices](#)

[Licensure and training needs](#)

[Patient safety](#)

[Ethical considerations and regulation](#)

[Conclusions and recommendations for next steps](#)

[Appendix A - Task force members and qualifications](#)

[Appendix B - Task force workgroups](#)

[Appendix C - Record of attendance](#)

[Appendix D - Summary of public comments](#)

[Appendix E - Evidence review description of methods](#)

[Appendix F - Annotated bibliography](#)

[Appendix G - Phase II evidence review](#)

[Appendix H - Training resources](#)

[Appendix I - Ethical and legal considerations of drug-assisted psychotherapy](#)

[References](#)

List of Abbreviations

Abbreviation	Definition
5D-ASC	5-Dimensions of Altered States of Consciousness
ADE	Adverse Drug Event
ANOVA	Analysis of Variance
APA	American Psychiatric Association
AUC	Area Under the Curve
AUDIT	Alcohol Use Disorder Identification Test
BDI	Beck Depression Inventory
BDNF	Brain-Derived Neurotrophic Factor
BPRS	Brief Psychiatric Rating Scale
CANMAT	Canadian Network for Mood and Anxiety Treatments
CAPS	Clinician-Administered PTSD Scale
CEU	Continuing Education Units
cGMP	Current Good Manufacturing Practices
CNS	Central Nervous System
COMP360	Compass Proprietary Psilocybin
COWS	Clinical Opioid Withdrawal Scale
CRP	C-Reactive Protein
CSA	Controlled Substances Act
DEA	Drug Enforcement Agency
DHD	Desire for Hastened Death
DHHS	Department of Health and Human Services
DMT	Dimethyltryptamine
DO	Doctor of Osteopathic Medicine
DOJ	Department of Justice
DRRC	Drug Regimen Review Center
DS	Demoralization Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSST	Digit Symbol Substitution Test
DUDIT	Drug Use Disorder Identification Test
EAT	Eating Attitudes Test
EQ-5D-3L	European Quality of Life 5 Dimensions, 3 Level
EQ-VAS	European Quality Of Life Visual Analog Scale
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
GAD-7	Generalized Anxiety Disorder Scale – 7 Items
GRID HAM-D	Revised Hamilton Rating Scale for Depression
HADS	Hospital Anxiety and Depression Scale

HADS-A	Hospital Anxiety and Depression Scale Patient Reported Anxiety
HADS-D	Hospital Anxiety and Depression Scale - Depression
HAM-A	Hamilton Anxiety Rating Scale
HAM-D	Hamilton Rating Scale for Depression
HIPAA	Health Insurance Portability and Accountability Act
HMHI	Huntsman Mental Health Institute
HPPD	Hallucinogen Persisting Perception Disorder
IL	Interleukin
LOM	Loss of Meaning
LSAS	Liebowitz Social Anxiety Scale
LS	Least Squares
LSD	Lysergic Acid Diethylamide
LSMD	Least Squares Mean Difference in Change from Baseline
LTFU	Long Term Follow-Up
MADRS	Montgomery-Åsberg Depression Rating Scale
MAPS	Multidisciplinary Association for Psychedelic Studies
MD	Doctor of Medicine
MDD	Major Depressive Disorder
MDMA	Methylenedioxymethamphetamine
MDMA HCl	Methylenedioxymethamphetamine Hydrochloride
MEQ	Mystical Experience Questionnaire
META	Motivational enhancement and Taking Action
MIPDTF	Mental Illness Psychotherapy Drug Task Force
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NDA	New Drug Approval
NEO PI-R	Neuroticism, Extraversion, and Openness to Experience Personality Inventory
OHA	Oregon Health Authority
OOWS	Objective Opioid Withdrawal Scale
OPAB	Oregon Psilocybin Services Act
PANAS	Positive and Negative Affect Schedule
PCET	Penn Conditional Exclusion Task
PDB	Psychotherapy Drug Board
PICOS	Population, Intervention, Comparison, Outcome, Study
POMS	Profile of Mood States
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-Traumatic Stress Disorder
QIDS-SR-16	Quick Inventory of Depression Symptomatology Self-Rated 16 Item Scale
QTcF	QT Interval Corrected Using Fridericia's Formula
RCT	Randomized Control Trial
REMS	Risk Evaluation and Mitigation Strategy

ROB	Risk of Bias
SADE	Serious Adverse Drug Event
SD	Standard Deviation
SDS	Sheehan Disability Scale
SE	Standard Error
SEM	Standard Error of the Mean
SMD	Standardized Mean Difference
SNRI	Serotonin and norepinephrine reuptake inhibitors
SOWS	Subjective Opioid Withdrawal Scale
SRR	Spontaneously Reported Reactions
SSRI	Selective Serotonin Reuptake Inhibitors
STAI	Spielberger State Trait Anxiety Inventory
SUD	Substance Use Disorder
TEAE	Treatment-Emergent Adverse Effects
TESAE	Treatment-Emergent Serious Adverse Event
TRD	Treatment Resistant Depression
UCA	Utah Cannabis Act
UGT1A9	Glucuronosyltransferase Family 1 Member 9
UGT1A10	Glucuronosyltransferase Family 1 Member 10
UMCA	Utah Medical Cannabis Act
WSAS	Work and Social Adjustment Scale

Executive Summary

The Mental Illness Psychotherapy Drug Task Force (MIPDTF) was established as a result of [H.B. 167 Mental Illness Psychotherapy Drug Task Force](#) during the 2022 General Session of the Utah Legislature. The purpose of the MIPDTF is to provide evidence-based recommendations on any controlled substance that: (a) is not currently available for legal use (i.e., schedule I controlled substance); and (b) may be able to treat, manage, or alleviate symptoms from mental illness. The task force was co-chaired by Dr. Michelle Hofmann, Utah Department of Health and Human Services (DHHS) Executive Director Tracy Gruber's designee, and Dr. Mark Rapaport, the chief executive officer (CEO) of the Huntsman Mental Health Institute (HMHI), included eleven experts as specified in statute, administrative staff from the DHHS and expert review of the literature provided by the [Drug Regimen Review Center \(DRRC\)](#) at the University of Utah.

Given to the short timeframe to complete the report and after an initial review of existing peer-reviewed evidence, the task force decided to focus its efforts on the two schedule I controlled substances where there was enough published data to allow a meaningful evaluation of their safety and efficacy in enhancing psychotherapy for specific psychiatric disorders, methylenedioxymethamphetamine (MDMA) and psilocybin. Both are under fast-track review by the Food and Drug Administration (FDA) and both are in a class of psychoactive substances that produce changes in perception, mood and cognitive processes known as psychedelics (also known as hallucinogens). Psychedelics affect all the senses, altering a person's thinking, sense of time and emotions. They can also cause a person to hallucinate—seeing or hearing things that do not exist or are distorted.

In order to meet legislative intent, the task force organized four workgroups represented by task force members to develop specific recommendations requested in H.B. 167. All requested recommendations are addressed in this report within the context of the most promising currently available evidence on MDMA for the treatment of post-traumatic stress disorder (PTSD) and psilocybin for the treatment of depression.

Overall, the evidence review conducted for this report suggests preliminary evidence indicating that MDMA-assisted psychotherapy employing the 40-hour Multidisciplinary Association for Psychedelic Studies (MAPS) protocol is more effective than placebo or low dose MDMA-assisted psychotherapy in decreasing symptoms of PTSD during acute treatment trials. The preliminary safety data are encouraging but incomplete at this time. The published clinical trial data also suggest that psilocybin-assisted psychotherapy,

employing a carefully specified intervention, may be more effective than placebo-assisted psychotherapy in acute treatment trials for treatment resistant depression (TRD) and in care at the end of life for patients with symptoms of depression and anxiety. Again, the preliminary safety data are encouraging but incomplete at this time. Finally, our initial review of the recent literature employing lysergic acid diethylamide (LSD), ayahuasca and ibogaine-assisted psychotherapy found there was not enough peer reviewed data to make any recommendations about either efficacy or safety.

While cannabis and psychedelic compounds are similar in their status as schedule I controlled substances regulated by the U.S. Drug Enforcement Administration (DEA), the MIPDTF recommendations are distinctly different from work that has been done with respect to medical cannabis in Utah. First, unlike cannabis, two different psychedelic substances have fast-track New Drug Approval (NDA) applications open with the FDA; therefore rigorous studies of safety and efficacy are ongoing. Second, an FDA advisory committee made up by national experts will be evaluating the data from these trials in support of their approval. Third, with any FDA approval will come regulations regarding manufacturing standards, administration, storage, and safety standards, which will be unique by compound and adds significant complexity to the establishment of such standards. Finally, the costs associated with implementing psychedelic-assisted psychotherapy ahead of FDA approval, which includes multiple preparatory, treatment, and integration psychotherapy sessions, far exceed those of medical cannabis.

Thus, the most rigorous and cost-effective approach to ensuring that the people of Utah have safe access to the most effective programs in psychedelic-assisted psychotherapy would be to wait for the fast-track FDA rulings for MDMA and psilocybin. FDA approval of the current NDA applications will also introduce a needed financing mechanism through government and commercial health insurance that will greatly offset costs to patients. (Of note, limited but defined pathways do exist today for patient access to psychedelic-assisted psychotherapy including patient participation in a clinical trial through the FDA Expanded Access Program and by a physician applying for compassionate use status through the FDA.) If this course is not taken and the Legislature decides to pursue making these substances available to the people of Utah as enhancements to psychotherapy, then, the extensive manufacturing, safety and regulatory guidelines outlined in this report should be followed. Two prerequisites to any such legislation recommended by the task force include: (1) a fiscal analysis of the one-time and the ongoing costs of developing a statewide program overseeing psychedelic-assisted psychotherapy to the taxpayers of Utah, and (2) development of a risk evaluation and mitigation strategy (REMS) for drug safety to help

ensure the benefits of psychedelic-assisted psychotherapy outweigh its risks and an assessment as to what governmental entity should be responsible for managing this part of the regulatory framework. If, over time, rigorous credible evidence emerges demonstrating other psychedelic substances can facilitate psychotherapy, then similar programs will need to be developed with the same degree of caution.

Sources indicate that we may see FDA approval for MDMA assisted-psychotherapy for the treatment of PTSD as soon as the end of 2023. While the task force believes it has completed the scope of work outlined in H.B. 167, reconvening ahead of the sunset date of January 1, 2024 to review the status of the FDA approval of any psychedelic drugs used to assist psychotherapy should occur to reassess new developments in the evidence and the task force's current recommendations.

Introduction

Task force history

The MIPDTF was established as a result of [H.B. 167 Mental Illness Psychotherapy Drug Task Force](#) during the 2022 General Session of the Utah Legislature.

Task force duties

The purpose of the MIPDTF is to provide evidence-based recommendations on any psychotherapy drug that the MIPDTF determines may enhance psychotherapy when treating a mental illness. This document fulfills a statutory requirement to submit, before October 31, 2022, a report to the Health and Human Services Interim Committee with specific recommendations as outlined in statute:

1. types or symptoms of mental illness for which the psychotherapy drug could be used as a treatment option,
2. the appropriate administration and dosage,
3. any license or credential required for an individual recommending or administering the psychotherapy drug,
4. training that may be helpful or should be required for an individual to recommend or administer the psychotherapy drug,
5. if an additional license or credential is recommended for prescribing or administering the psychotherapy drug, the administration of the license or credential,
6. the frequency at which the psychotherapy drug may be used,
7. any procedures to appropriately obtain, store, and monitor the use of the psychotherapy drug, potential psychotherapeutic modalities with which a psychotherapy drug may be used,
8. any organizations that may be able to provide a perspective on ethical considerations regarding the psychotherapy drug,
9. any safety requirements regarding the psychotherapy drug,
10. any necessary follow up procedures that should be followed after an individual takes the psychotherapy drug, any procedures for data tracking,
11. any additional investigation or research needed for the psychotherapy drug,
12. any long term societal impacts on the administration of the psychotherapy drug, and

13. proposed regulations the Legislature should consider if the psychotherapy drug is made legal for treating mental illness.

Task force structure

H.B. 167 requires the MIPDTF to be chaired by the DHHS executive director or the executive director's designee; and the CEO of the HMHI at the University of Utah. (Appendix A - Task force members and qualifications). Additionally, the task force is required to consist of the following members jointly appointed by the co-chairs as outlined in statute:

1. a licensed psychiatrist;
2. a licensed psychologist;
3. a licensed pharmacist;
4. a representative from the Utah Medical Association;
5. an individual who researches and studies neuroscience and mental health;
6. a representative from a Utah hospital or a major healthcare system;
7. a patient who is knowledgeable about the use of a psychotherapy drug, nominated by a patient advocacy group;
8. a trauma focused therapist;
9. a licensed attorney with knowledge of the law regarding controlled substances and other drugs;
10. a medical or psychiatric ethicist with knowledge of the ethical and legal issues pertaining to psychotherapy drugs; and
11. a clinician who is board certified in addiction medicine.

Members of the public who desired to be considered for MIPDTF selection were asked to apply by submitting a letter of interest and their CV or resume by contacting DHHS or through the [Governor's Boards and Commissions website](#). Applicants who submitted this information were considered and jointly appointed by the co-chairs as outlined in statute. Where statute required members of the MIPDTF to represent an organization, DHHS staff reached out to the executive director for their desired representative. In situations where members of the public did not submit an application, the co-chairs of the MIPDTF reached out to individuals known to meet specific membership criteria. These individuals were asked to submit their CV or resume and were considered and jointly appointed by the co-chairs as outlined in statute.

Task force meetings

The MIPDTF began meeting on May 31, 2022 and continued to meet at least monthly in a hybrid format. All meetings were open to the public and held in compliance with the Utah Public Meetings Act (Appendix C - Record of attendance). All meetings were available via Zoom or in person at the Multi Agency State Office Building, rooms 1019 A/B. Meeting documents, minutes, and recordings are available on the Utah Public Notice website: <https://www.utah.gov/pmn/sitemap/publicbody/7693.html>

All meetings of the MIPDTF provided an opportunity for public comment for fifteen minutes at the end of the agenda (Appendix D - Summary of public comments). Comments were limited to a maximum of three minutes per individual and anyone interested in providing public comment required a conflict of interest form signed and filed prior to offering comments. Written comments are also welcome at psychotherapytaskforce@utah.gov.

Task force workgroups

The MIPDTF members created and volunteered to join workgroups based on levels of expertise and experience in four identified areas of emphasis (Appendix B - Task force workgroups). The MIPDTF workgroups met as necessary in order to meet the requirements of H.B. 167. Workgroups meetings, because they did not include a quorum of the MIPDTF, are not subject to Utah's Open and Public Meetings Act.

Evidence review process

The purpose of the MIPDTF is to provide evidence-based recommendations on any schedule I controlled substance that the task force determines may enhance psychotherapy when treating a mental illness. The evidence review was performed by the [DRRC](#) at the University of Utah College of Pharmacy using evidence synthesis experts under an existing contract with the Utah Medicaid Pharmacy Program.

The key objective of the review was to perform as comprehensive a review as possible within the time constraints of H.B. 167. The DRRC uses the PICOS approach, commonly used in evidence synthesis for describing a focused research question based on five components (psilocybin is used as an exemplar below):

1. Population (e.g., patients with depression or anxiety)
2. Intervention (e.g., psychotherapy with psilocybin)
3. Comparison (e.g., psychotherapy without psilocybin)

4. Outcome (e.g., safety or efficacy measures)
5. Study design (e.g., experimental trials)

A preliminary search queried clinical trials registered in the U.S. (using ClinicalTrials.gov) studying use of various schedule I controlled substances for the treatment of a mental health condition. A candidate list of schedule I controlled substances and specific mental health conditions was created for a more focused evidence review from the ClinicalTrials.gov search results, and input from the MIPDTF members based on their knowledge of the current state of the evidence. Schedule I controlled substances selected include psilocybin, MDMA, LSD, ayahuasca, and ibogaine. The mental health conditions selected include depression, anxiety, PTSD, substance use disorders (SUDs), and demoralization associated with chronic disease.

The review process proceeded in two phases:

1. Phase I – Conduct a systematic search for experimental studies (e.g., randomized controlled trials) indexed in two bibliographic databases (Medline and Embase) or ClinicalTrials.gov that evaluate the use of the candidate list of Schedule I controlled substances in each of the five mental health conditions identified and prepare an annotated bibliography by June 30, 2022.
2. Phase II – Conduct a systematic search in additional relevant bibliographic databases (PsycINFO and the Cochrane Central Register of Controlled Trials [CENTRAL]) and prepare a report by September 30, 2022 that summarizes a qualitative evidence synthesis of safety, efficacy, and risk of bias assessment for the substances that had a sufficient body of evidence to allow a valid PICOS evaluation of the substance : mental health condition pairs identified in Phase I. The focus of Phase II was MDMA for PTSD and psilocybin for depression.

For a more detailed description of the methods used by the DRRC to complete the evidence review, see Appendix E - Evidence review description of methods.

Highlights from evidence review

Preliminary evidence indicates that MDMA-assisted psychotherapy employing the 40-hour MAPS protocol is more effective than placebo or low dose MDMA-assisted psychotherapy in decreasing symptoms of PTSD and during acute treatment trials and that psilocybin-assisted psychotherapy, employing a carefully specified intervention, may be more effective than placebo-assisted psychotherapy in acute treatment trials for treatment resistant depression (TRD) and in care at the end of life for patients with symptoms of depression and anxiety. The preliminary safety data for both substance : mental health

condition pairs are encouraging but incomplete at this time. Insufficient evidence exists to make recommendations about efficacy or safety for LSD, ayahuasca and ibogaine-assisted psychotherapy.

ClinicalTrials.gov search results

The results of this search show that MDMA is the controlled substance with a potential benefit for the treatment of mental illness that is the furthest along in clinical development, having at least one completed phase 3 study of MDMA-assisted therapy for the treatment of PTSD. Other controlled substance : mental health condition pairs next furthest along in clinical development with at least one or more *completed* phase 2 trials include LSD for illness-related anxiety; MDMA for cancer-associated anxiety and social anxiety disorder; and psilocybin for treatment-resistant depression, major depressive disorder, and cancer-associated psychological distress (eg, anxiety and depressive symptoms).

Annotated bibliography

The annotated bibliography included 43 records (Appendix F - Annotated bibliography). The majority of citations were for MDMA (n=18, 41.9%), followed by psilocybin (n=16, 37.2%). Included citations addressed seven unique trials for MDMA and psilocybin, two for LSD, and one each for ayahuasca and ibogaine. The studied mental health conditions varied by controlled substance. For MDMA, the most common was PTSD (n = 5 trials; 71.4 of unique MDMA trials), and for psilocybin, it was major depressive disorder (n = 3 trials; 42.9% of unique psilocybin trials) and psychological distress (e.g., depression, anxiety) associated with cancer (n = 3 trials; 42.9% of unique psilocybin trials). For LSD, ayahuasca, and ibogaine, included references were for one condition each: anxiety associated with life-threatening illness, major depressive disorder, and management of withdrawal in people receiving opioid substitution therapy, respectively.

MDMA-assisted therapy for PTSD

Evidence from one phase 3 randomized controlled trial (RCT) (n=90) supports MDMA-assisted therapy as an effective option for people with chronic, severe PTSD.⁵ The phase 3 trial results are supplemented by seven small phase 2 trials among people with moderate to severe, chronic PTSD.⁶⁻¹² Available evidence is most applicable to people with severe PTSD that have failed at least one first-line PTSD treatment and lack severe medical comorbidities. The phase 3 trial included participants with dissociative PTSD, and preliminary evidence suggests MDMA-assisted therapy is at least similarly effective in this subpopulation.⁵ Many participants in the phase 3 trial also had major depressive disorder (MDD) with a lifetime history a suicidal ideation.⁵ Trials also enrolled participants with diverse trauma histories, supporting potential use of MDMA-assisted therapy for civilian and veteran populations.^{5,15} Few people included in RCTs were diagnosed as having

moderate PTSD symptoms at baseline,¹⁵ though there is an ongoing phase 3 trial evaluating MDMA-assisted therapy for this population.³⁹ Limitations of the available RCT evidence are the relatively small sample size, homogenous population, and the possibility of an overestimate of benefits and underestimate of risks, primarily due to possible attrition bias and confounding bias from unblinding of participants and therapists to treatment allocation. It is important to keep in mind that the evidence reviewed for this report is limited to the MAPS-sponsored formulation of MDMA, and the evidence in favor of safety of efficacy may or may not extend to other MDMA formulations.

Safety information from relatively short-term (maximum of approximately 12 months) follow-up have not demonstrated an increased risk of severe adverse events for most participants.^{5,15} Though, enrolled participants were at lower risk for severe adverse events based on the absence of psychotic disorders, active substance use disorders (exceptions were mild disorders, moderate disorders in early remission or cannabis use disorder),⁸¹ and uncontrolled or severe cardiovascular disease at baseline.^{5,15}

Delivery of MDMA-assisted therapy using the model from the phase 3 RCT requires at least two trained therapists (eg, having at least a master's degree and trained on the MDMA-assisted therapy model) for each person receiving the treatment. To complete MDMA-assisted therapy as studied in the phase 3 trial, the therapists and participants must be available for approximately fifteen therapy sessions totaling over 40 hours.⁵ Additionally, close monitoring for psychiatric and medical adverse events in a safe, controlled setting is required during the MDMA-assisted therapy sessions.⁹⁰ In clinical trials, most participants stayed with an attendant at the treatment facility the night after receiving MDMA.⁵

The non-profit organization sponsoring these trials, MAPS, hopes to submit evidence for approval of MDMA-assisted therapy for PTSD to the FDA in 2023 once top-line results from the second phase 3 trial are available.⁹¹ If successful, it is projected that FDA approval could be granted around May 2024.⁹²

The overall body of evidence reviewed by this report supports a significant benefit from MDMA-assisted therapy for severe chronic PTSD. However, the direction of potential biases tends to be nonconservative, meaning that it is likely that the magnitude of the efficacy estimate is overestimated, and that risks are underestimated. Relative consistency of the benefits of MDMA-assisted therapy across the included RCTs and the large treatment effect size decreases the likelihood that the biases could be explaining all of the benefit, but there is greater uncertainty about potential risks. Results of additional well-designed trials, and longer follow-up, could improve our understanding of the magnitude of benefit and risks of treatment.

Psilocybin-assisted therapy for major depressive disorder and treatment-resistant depression

Results from three RCTs offer preliminary positive support for psilocybin-assisted therapy (administered over 1-2 sessions) as a short-term treatment for moderate to severe MDD and TRD.¹⁶⁻¹⁸ The small trial by Davis et al did not use an adequate control group to distinguish the effect of psilocybin (plus psychological support sessions) from psychological support alone,¹⁸ and the other trial among people with MDD by Carhart-Harris et al failed to demonstrate significant symptom reduction over a commonly used antidepressant, escitalopram.¹⁶ The RCTs among people with MDD were limited by the unblinded trial design (Davis et al) or high-risk for unblinding of participants and personnel (Carhart-Harris et al), lack of standardization of psychological support, short follow-up, small sizes (Carhart-Harris et al and Davis et al), and relatively homogenous study populations.¹⁶⁻¹⁸ Nonetheless, the trends of these studies, along with statistically significant benefit for TRD symptoms in the 3rd trial,¹⁷ suggest positive effects by psilocybin for depression and offer motivation to conduct additional larger phase 3 trials.

Current evidence is most applicable to adults with moderate to severe unipolar major depression without severe medical comorbidities that do not have a condition that might interfere with establishing a patient-therapist rapport (e.g., some personality disorders). There is a lack of information for use of psilocybin-assisted therapy among people with high-risk conditions such as psychotic disorders, active substance use disorders, or high suicidality risk.¹⁶⁻¹⁸ Overall long-term follow-up data is limited, with only the smallest trial (n=24) having published observational follow-up for twelve months after treatment¹⁰²; however, more robust definitions for maintenance of effect than were used by the follow-up study seem warranted to make firm claims of a stable or durable effect of by psilocybin-assisted therapy.

During the 3 trials, most adverse events associated with psilocybin were transient, occurring most frequently on the day of psilocybin dosing.¹⁶⁻¹⁸ Headaches and nausea occurred frequently but tended to be mild to moderate in severity.^{16,17} Serious adverse events were not observed in the two smaller trials (n=24 to 59).^{99,100} However, serious adverse events, including instances of severe suicidal ideation and/or suicidal behaviors tended to occur more frequently with the higher psilocybin doses (10-25 mg) compared to psilocybin 1 mg in the largest trial (n=233).¹⁷ Nevertheless, the safety profile of higher doses of psilocybin generally compared favorably to escitalopram over six weeks.¹⁶ Unfortunately, the Davis et al trial did not report adverse events for each arm during the controlled phase of the study.¹⁸

Psilocybin-assisted therapy could offer an additional option for the armamentarium of depression treatments. An advantage of psilocybin-assisted therapy is that it does not require daily administration like an oral antidepressant. Additionally, psilocybin-assisted therapy may serve as an option for more difficult-to-treat cases (i.e., those who failed at least two antidepressants) based on evidence from a single short-term RCT.¹⁷ However, additional larger confirmatory trials to compare psilocybin-assisted therapy to

pharmacotherapy and/or evidence-based psychotherapy are needed. While psilocybin-assisted therapy is a promising experimental treatment for depression, the existing evidence is limited by bias threats (eg, expectancy bias from lack of blinding¹⁸ or unblinding of participants,¹⁶ and possible attrition bias for two of the three trials^{17,18} including the largest one) that tend to lead to exaggerated treatment effect sizes. In addition, the two smaller trials lacked information about training and standardization of psychological support,^{16,18} an important part of the psilocybin-assisted therapy intervention, which had an unknown impact on the trial outcome.

In July and August 2022, the American Psychiatric Association (APA) and Canadian Network for Mood and Anxiety Treatments (CANMAT) both issued recommendations or position statements on the use of psychedelic agents for the treatment of psychiatric conditions¹⁰⁹ or MDD.¹¹⁰ Both organizations determined that there is insufficient evidence to recommend psilocybin for the treatment of MDD outside of a clinical trial.^{109,110} In Canada, psilocybin-based treatment may be allowed as a compassionate use for serious, life-threatening illness in rare cases.¹¹⁰ Neither statement appeared to have considered the results from the COMPASS-sponsored phase 2b trial for TRD; nevertheless, it seems unlikely that this unpublished trial would change their recommendations. The APA statement urged conducting evidence-based research and maintaining current regulatory standards (i.e., FDA approval) before recommending treatments.¹⁰⁹ The FDA has granted breakthrough therapy designation for psilocybin-assisted therapy to two organizations,^{111,112} but the trials needed to submit for FDA approval are still ongoing.

Indications and prescribing practices

In addition to offering specific recommendations on the promising schedule I controlled substance : mental health condition pairs informed by the evidence review, the Indications and Prescribing Practices workgroup reviewed emerging best practices to inform a principled approach. The specific recommendations outlined in H.B. 167 addressed by this workgroup include:

- Appropriate administration and dosage
- Frequency drug may be used
- Potential psychotherapeutic modalities with which drug may be used
- Any necessary follow up after an individual takes drug

Any program that supports the prescribing and administration of psychotherapy drugs to enhance psychotherapy should:

- I. **Use a multidisciplinary team approach.**
 - A. All team members should receive requisite and sufficient training with appropriate oversight (see Licensure and Training Needs).
 - B. Prescribing should be conducted by an MD or DO

- C. Prescribers should work closely with the mental health therapist / therapist team to ensure seamless communication during the therapeutic course, including any adverse events in treatment.
- D. Where possible, pre-existing and established mental health providers should be involved in shared decision-making surrounding engagement with a course of treatment with a psychotherapy drug.
- II. Provide flexible pathways for patient access that consider financial barriers.**
 - A. Patients should be referred by a clinician.
 - B. Equity in access to a costly treatment program that includes multiple psychotherapy sessions should be addressed in any program design.
- III. Prevent opportunities for harm.**
 - A. All patients should be screened for medical and psychiatric contraindications. This may include laboratory testing and an electrocardiogram.
 - B. Children under 18 should be excluded from treatment.
 - C. Drug administration sessions should provide continuous, in-person psychotherapeutic support.
 - D. A support person and transportation to and from sessions should be pre-arranged.
 - E. Treatment of individuals in unstable environments may exacerbate their mental health conditions. Care should be taken to ensure adequate psychosocial supports are in place prior to initiating any treatment course. This should include evaluation and consideration of:
 - 1. Stable and safe housing environment
 - 2. Stable and secure interpersonal relationships
 - F. Vital signs should be monitored during drug administration sessions.
 - G. Comprehensive education must be provided to the patient receiving treatment with regard to safety and efficacy of this treatment, including post-administration monitoring requirements. Signed patient consent must be obtained prior to administration with regard to these safety, efficacy, and monitoring standards.
- IV. Emphasize the psychotherapeutic process using evidence-based indications and psychotherapy modalities.**
 - A. Psychotherapy processes should be conducted in-person by trained and certified clinician(s).
 - B. Initial medical use of psychotherapy drugs to enhance psychotherapy should be restricted to indications with the most established evidence base, subject to ongoing review and revision as new evidence emerges.

Additional in-office procedures and best practices that must be considered include:

- I. Strict procedures for drug administration and storage.**
 - A. Drug administration should be on-site in a supervised fashion with at least one mental health therapist present for the duration of the session.

1. Regardless of the number of clinicians present, video recording in a HIPAA-compliant fashion of all active drug sessions should be included.
 2. REMS or REMS-style oversight program for prescribing and administration of psychotherapy drugs to enhance psychotherapy is recommended.
- B. Drug storage and prescribing should follow DEA Schedule I requirements (subject to change in the context of DEA rescheduling) and include a log of custody, drug handling and administration in accordance with these standards.

II. Patient tracking and documentation.

- A. A centralized mechanism for patient tracking that includes (at a minimum) indication, dosage, and prescriber should be established.
- B. As noted above in III.G., comprehensive education must be provided to the patient receiving treatment with regard to safety and efficacy of this treatment, including post-administration monitoring requirements. Signed patient consent must be obtained prior to administration with regard to these safety, efficacy, and monitoring standards.

III. Advance preparations before drug administration ('set and setting').

- A. Prior to any drug administration session there should be robust preparation, including psychoeducation regarding the session itself, drug effects, possible side effects, and anticipated challenges.
- B. Rapport should be built with the patient so they are comfortable with the therapist team.
- C. Expectations should be set regarding treatment and treatment course. This should involve at least one preparation session prior to an active drug administration session.
- D. Sessions should be conducted in a 'living room environment'.
 1. Sessions should take place in a comfortable environment with close access to a restroom.
 2. A music playlist and eyeshades should be available.
 3. Patients can be invited to bring personally meaningful or spiritually meaningful items to the sessions.
 - a) Overt spiritual or religious iconography unless directed by the patient in concordance with their own faith based traditions should be avoided.
- E. 'Rescue' medications should be available for any adverse events in session:
 1. Promethazine 12.5-25 mg for nausea.
 2. Ibuprofen 600 mg and/or acetaminophen 650 mg for headache.
 3. Clonidine 0.05-0.1 mg for sustained clinically significant hypertension.
 4. Lorazepam 1-2 mg for clinically significant anxiety with distress deemed non-therapeutic.

Proceeding in the absence of FDA approval

In the absence of FDA authorization for the use of specific drugs to enhance psychotherapy for specific mental health conditions, should the Legislature decide to pursue making psychedelic substances available to the people of Utah as enhancements to psychotherapy there are several specific indications and exclusion criteria that are recommended.

MDMA-assisted psychotherapy for PTSD

An emerging and robust evidence base from Phase II and initial Phase III trials is supported by a Multidisciplinary Association for Psychedelic Studies (MAPS) protocol with manualized psychotherapy that serves as a model for MDMA-assisted psychotherapy in the treatment of PTSD. Specific protocol requirements include:

1. 40 hour therapy protocol with three preparatory sessions, three MDMA-assisted therapy sessions with three integration sessions between each MDMA session.
2. Two therapists present per participant for the duration of the therapeutic protocol.
3. Established training program (MAPS).
4. Core principles of manualized therapy (supportive in nature): *Safety, Support, Inner Healing Intelligence, Inner-directed process, Beginner's Mind, Trusting the Process, Somatic Manifestation, Therapeutic Alliance and Trust.*
5. MDMA dosage: Initial dose of 80-125 mg + possible 40-62.5 mg booster at 1.5-2 hour.
 - a. Dosage adjustments can be made in a clinically informed fashion depending on patient response.
 - b. Recommend lower initial dose in the following contexts: clinical uncertainty regarding response, acuity of psychiatric presentation, availability of intact support systems surrounding treatment, medical comorbidities, lower body weight, no prior personal experience with MDMA or classic psychedelics.
 - c. Recommend starting with lower doses.
6. Vital sign monitoring at baseline and every 30 minutes through 4 hours then hourly until 8 hour mark.

Exclusion criteria for MDMA-assisted psychotherapy include but are not limited to:

1. History of psychosis, diagnosis of a psychotic disorder, bipolar disorder type I, significant family history of psychosis or psychotic disorder, cluster B personality disorder, dissociative identity disorder, unstable substance use disorder or alcohol use disorder, active suicidal ideation, severe depression requiring inpatient level of care.
2. Concurrent use of serotonergic medications (SSRIs, SNRIs), concurrent use of any psychostimulants (including modafinil).
3. Serious cardiovascular disease (congestive heart failure, cardiac ischemia, angina pectoris), advanced liver disease, uncontrolled hypertension, history of seizure, history of stroke, prolonged QT, history of serious cardiac arrhythmias, renal insufficiency as defined by creatinine clearance < 40 calculated by Cockcroft-Gault formula.

4. Pregnancy or breastfeeding.
5. Insufficient psychosocial or interpersonal support to sustain an intensive treatment protocol.

Psilocybin and depression

Psilocybin-assisted therapy for three categories of depression have an emerging evidence base: (1) Major Depressive Disorder (MDD), (2) Treatment Resistant Depression (TRD), and (3) symptoms of anxiety and depression associated with terminal illness. Specific protocol requirements include:

1. Associated psychotherapy process with 2-3 preparatory sessions (1-2 hours each), 1-3 dosing sessions with support (8 hours each), and 2-3 integration sessions (1-2 hours each).
2. Dosing session 8 hours.
3. Psilocybin dosing 25-40mg. Weight-based strategies suggest 22mg/70kg to 30mg/70kg. Recommend starting with lower doses.
4. Vital sign monitoring at baseline and every 30 minutes through 4 hours then hourly until 8 hour mark.

Exclusion criteria for psilocybin-assisted psychotherapy include but are not limited to:

1. History of psychosis, diagnosis of a psychotic disorder, bipolar disorder type I, significant family history of psychosis or psychotic disorder, cluster B personality disorder, dissociative identity disorder, unstable substance use disorder or alcohol use disorder, active suicidal ideation, severe depression requiring inpatient level of care.
2. Serious cardiovascular disease (congestive heart failure, cardiac ischemia, angina pectoris), advanced liver disease, uncontrolled hypertension, history of seizure, history of stroke, prolonged QT, history of serious cardiac arrhythmias, renal insufficiency as defined by creatinine clearance < 40 calculated by Cockcroft-Gault formula.
3. Pregnancy or breastfeeding.
4. Insufficient psychosocial or interpersonal support to sustain an intensive treatment protocol.

Additional possible indications under compassionate or palliative use

Additional indications could be determined on a case-by-case analysis by a 'compassionate use' board through direct clinician referral only. These possible indications should be reviewed according to new emerging evidence but also in the context of case-by-case situations of treatment-refractory conditions causing significant suffering or disability. These conditions may include the following indications; however, exclusion criteria and excluded diagnoses detailed above continue to apply (e.g., significant risk of psychosis or mania).

1. Substance and alcohol use disorders refractory to standard of care evidence-based medications and therapies.
2. Treatment-refractory obsessive compulsive disorder.
3. Treatment-refractory anorexia nervosa.
4. Treatment-refractory chronic pain conditions.

Licensure and training needs

Training programs, associations, universities and ongoing research efforts contribute to a growing body of best practices for training and certification requirements for integrative psychotherapy. To compile their recommendations, the Licensure and Training Needs workgroup reviewed various research protocols, national association reports, and specific licensure and training procedures from more than a decade of psychedelic prescribing and medicine-assisted psychotherapy laws, policies, protocols, and training and certification procedures created, implemented, researched and refined in the United States and other nations. In addition, lessons learned from ketamine's use in integrative psychotherapy and the more recent implementation of Utah's Center for Medical Cannabis and the state of Oregon's Psilocybin Act help inform future psychedelic medicine rulemaking and protocols. The specific recommendations outlined in H.B. 167 addressed by this workgroup include:

- Any license or credential required
- Training that may be helpful or should be required
- If an additional license or credential is recommended, procedures for administration of the license or credential

The Licensure and Training Needs workgroup provides the following recommendations:

- I. The Utah Legislature should provide parameters in Utah law to create a Psychotherapy Drug Board (PDB) within DHHS.**
 - A. The PDB should advise DHHS in its promulgation of administrative rules and procedural policies for prescribing and psychotherapy training, certification, and continuing education as well as a monitoring process.¹
 - B. The membership of the PDB could be similar to MIPDTF membership.
- II. The PDB should establish and maintain a certification process for licensed prescribers² as defined in Utah laws and rules and certified by the PDB as**

¹ The Utah Division of Occupational and Professional Licensing shall continue to administer and enforce specific laws related to the licensing and regulation of professionals.

² Should the Legislature proceed in establishing psychedelic-assisted psychotherapy programs in Utah ahead of any FDA approval, as schedule I controlled substances, psychedelics cannot be

specially trained in mental health prescription practices to provide psychedelic drug recommendations.

- A. Certification should be required for any individual prescribing or administering psychotherapy drugs and restricted to licensed physician prescribers only.
- B. The administration of certification should be established and maintained by the PDB with administrative support through DHHS.
- C. Requirements for certification should include specialized training for an individual to prescribe or administer the psychotherapy drug.
- D. Qualifications for certification should include demonstration of a minimum of two years mental health prescription practice and/or demonstration of specialized training or licensure in mental health prescription practices as outlined and updated according to best practices established by the PDB and promulgated in rules by DHHS.
- E. The PDB should outline a certification renewal process to include a minimum number of hours and qualified Continuing Education Units (CEUs) yearly.
- F. Monitoring and data tracking should be conducted through the creation and maintenance of a database of certified providers within DHHS.

III. The PDB should establish and maintain a certification process for “Mental Health Therapists” as defined in Utah Code Ann. 58-60-102(5) Mental Health Professional Practice Act to administer Psychedelic Psychotherapy.

- A. Certification should include minimum hours of PDB-approved psychedelic psychotherapy training (typically 80-120 hours). National and International Training programs may be considered for approval by the PDB.
- B. Two years post-licensure clinical experience should be required prior to application for Psychedelic Psychotherapy certification. Consideration should be given by the PDB for provisional certification under the supervision of a provider who has been certified and practicing for at least two years.
- C. The PDB should outline a certification renewal process to include a minimum number of hours and qualified CEUs yearly.
- D. Monitoring and data tracking should be conducted through the creation and maintenance of a database of certified providers within DHHS.

IV. The PDB should advise DHHS about the establishment of minimum standards for psychedelic psychotherapy service delivery for inclusion in administrative rules that would include:

prescribed like other drugs. A model similar to Utah’s Center for Medical Cannabis, where prescribers ‘recommend’ cannabis would be appropriate to address this concern.

- A. Guidelines for “set and setting” and minimum number of preparatory therapy sessions and/or indicators of preparedness such as previous treatment sessions, progress in treatment, severity of symptoms and other clinical safety indicators.
- B. Therapeutic support during psychotherapy drug administration, including guidelines for spacing and number of sessions based on current best practice, progress in treatment and other clinical indicators.
- C. Minimum number of integrative sessions and/or indicators of progress in treatment, safety and other clinical indicators.

V. Related Recommendations.

- A. The PDB should establish training requirements as part of certification for both physician prescribers and psychotherapists that include specific ethics best practices (e.g., ethical boundaries training) to help ensure patient safety.
- B. The PDB should establish and maintain an approved training resource list from existing and emerging reputable providers to be published through DHHS for physician prescribers and psychotherapist certification. See [Appendix E](#) for current examples (not vetted or approved for quality).³
- C. The PDB should outline the ability for DHHS to audit physician prescriber and psychotherapist credentials, treatment records and onsite compliance with Utah laws and rules and DHHS protocols.
- D. In the case of a physician prescriber recommending and administering the psychotherapy drug(s) and providing psychotherapy, both certifications should be obtained.
- E. Paraprofessionals, including certified peer support specialists, should be considered by the PDB, in accordance with emerging best practices, as potential support personnel during psychotherapy drug administration, preparatory and integration support.
 - 1. The PDB should establish training and certification for paraprofessional staff in accordance with emerging best practices and should establish protocol and advise DHHS about language for administrative rules that structures paraprofessional practice only as part of a treatment team, including clinical supervision by certified

³ At present MDMA-assisted psychotherapy requires certification from the MAPS Therapy Training Program in MDMA-assisted therapy for PTSD. It is possible other authorized training programs will become available. These will be reviewed and approved by the PDB.

prescribers and/or mental health therapists certified in psychedelic psychotherapy.

- F. In the case of FDA approval for psychotherapy drugs overseen by the PDB, existing certification and training requirements and resources, audit processes and the database of certified providers should be maintained and adapted to align with federal law.

Patient safety

Complementing the work of the Indications and Prescribing Practices workgroup, the Patient Safety workgroup delved more deeply into several topical areas relevant to keeping patients safe. Using the model of the 'package insert', a standard for all FDA-approved drugs, additional safety considerations are enumerated below. Should the Legislature decide to pursue making psychedelic substances available to the people of Utah as enhancements to psychotherapy ahead of FDA authorization, since the standard package insert information would not be available, the workgroup recommends the development of a patient handout that outlines this safety information in a patient friendly format that must be distributed with each drug dispensing / administration. The specific recommendations outlined in H.B. 167 addressed by this workgroup include:

- Any safety requirements regarding drug
- Any procedures to appropriately obtain, store, and monitor use
- Any procedures for data tracking

MDMA

Warnings and precautions

- Repeated chronic exposure to high doses of MDMA have the potential to reduce regional serotonin, damage serotonin axons and cause neurotoxicity. The risk of CNS neurotoxicity within an intended clinical dosing regimen appears to be minimal.
- Spontaneously reported reactions (SRR) of MDMA HCl in low dose applications (25-40 mg) are similar to rates seen in placebo groups in MDMA assisted therapy for PTSD treatment. The rate of SRR increases dramatically with higher doses (75-150 mg). SRRs were typically observed during drug administration, diminished as the drug was metabolized, with the majority of reactions resolving within several days and up to one week after dosing.

Adverse reactions

- Common adverse drug events (ADEs) of MDMA reported in Phase 1 studies in healthy volunteers include elevation in blood pressure and heart rate, increased

anxiety or dysphoria, and dilated pupils. Some reports indicated decreased rather than increased alertness. Other common ADEs reported in controlled studies of MDMA include reduced appetite, dizziness, tight jaw, bruxism (tooth-grinding), disturbance in attention, impaired gait or balance, dry mouth, and thirst. Participants in some studies also reported or exhibited changes in cognition, such as increases in speed of thought or thought blocking, facilitated imagination or recall, and unusual thoughts or ideas. Other less commonly reported events include paraesthesia (unusual body sensations) such as tingling or feeling hot or cold. MDMA can produce anxiety in healthy volunteers. A greater incidence of diarrhea, muscle tightness, and impaired judgment were reported. These effects are transient and recede as drug effects wane.

- The subset of ADEs referred to as SSRs included: anxiety, depressed mood, insomnia, obsessive rumination, restlessness, irritability, headache, disturbance in attention, dizziness, paresthesia, judgment impaired, hypersomnia, nausea, diarrhea, fatigue, asthenia, feeling cold, muscle tension, decreased appetite, hyperhidrosis, disturbed gait, dry mouth, thirst, sensation of heaviness, somnolence, and nystagmus.

Drug interactions

- Metabolism of MDMA is complex, with 50-75% of the parent compound being metabolized. Major enzymes involved in metabolism of MDMA include: CYP2D6 (>30%)> CYP1A2>CYP3A4>CYP2C19> CYP2B6. Active doses of MDMA HCl (75 mg - 125 mg) reversibly inhibit CYP2D6 and decrease CYP3A4 activity, with CYP2D6 activity normalizing after ten days post-drug. In the therapeutic dose range of 75-125 mg MDMA HCl, a concentration-dependent effect is observed. Thus the concentrations of medications metabolized via these hepatic enzyme systems may be elevated after MDMA administration for up to ten days.
- Several drug classes (MDMA metabolites or analogs, anesthetics, muscle relaxants, amphetamines and stimulants, benzodiazepines, ethanol, opioids), four antidepressants (bupropion, sertraline, venlafaxine and citalopram) and olanzapine demonstrated increased odds ratios for the reported risk of death.

Use in specific populations

- Pregnancy - Research suggests that MDMA may have adverse effects on the developing fetus. This includes the impact of hyperthermia and anorexia. Issues in the fetus can include premature birth, developmental issues, and cardiovascular issues (all seen in recreational not therapeutic use). One study in humans showed that prenatal MDMA exposure was associated with motor delays in the offspring up to two years after birth. More research is needed to determine if these delays persist later in life. Therefore, MDMA assisted treatment should not include individuals who are pregnant.

- Lactation - Research has demonstrated that MDMA does transfer into breast milk. Recommendations are that a 48 hour withholding period for breastfeeding is recommended following ingestion of MDMA.
- Females and Males of Reproductive Potential - No information available. A negative pregnancy test should be required prior to administering MDMA.
- Pediatric use - No information available.
- Geriatric use - No information available.
- Hepatic impairment - No information available.

Drug abuse and dependence

- Recommendations should include those found for Schedule I controlled substances.
- Currently MDMA is Schedule I, indicating a potential for abuse. Experiments have shown that animals will self-administer MDMA, indicating addictive potential. However, there is no evidence that limited therapeutic use leads to substance abuse.
- Data from both humans and animals suggest that regular, chronic MDMA use produces adaptations in the serotonin and dopamine systems that are associated with substance use disorder and related behaviors, such as increased impulsivity. There have been reports of MDMA use leading to symptoms of addiction, including continued use despite negative physical or psychological consequences, tolerance, withdrawal, and craving. There is no evidence that limited therapeutic use results in dependence.

Overdosage

- In high doses, MDMA can interfere with the body's ability to regulate temperature. On occasions, this can lead to a sharp increase in body temperature (hyperthermia), resulting in liver, kidney, and cardiovascular system failure, and death. Because MDMA can interfere with its own metabolism, potentially harmful levels can be reached by repeated drug use within short intervals.

Psilocybin

Warnings and precautions

- Avoid in contraindicated psychological conditions or interacting medications.

Adverse reactions

- Suicidal ideation (individuals who did not respond to treatment).
- Acute elevations of fear and anxiety, panic, delusion and cognitive impairments at higher doses (>25 mg oral).

Drug interactions

- Glucuronosyltransferase family 1 member 9 and 10 (UGT1A9 and UGT1A10) inhibitors should be discontinued at least five half-lives prior to administration.
- Monoamine Oxidase Inhibitors, Acetaldehyde Dehydrogenase Inhibitors and Alcohol Dehydrogenase Inhibitors should be discontinued at least five half-lives prior to the administration.

Use in specific populations

- Pregnancy - There are no human case reports or studies with psilocybin in pregnancy. It is recommended that psilocybin be avoided in pregnancy. A negative pregnancy test is required the morning prior to administration of treatment with psilocybin.
- Lactation - No information available.
- Females and Males of Reproductive Potential - No information available. A negative pregnancy test is required prior to administering psilocybin.
- Pediatric use - No information available.
- Geriatric Use -No information available.
- Hepatic Impairment - No information available.

Drug abuse and dependence

- Recommendations should include those found for Schedule I controlled substances.
- Currently psilocybin is Schedule I, indicating a potential for abuse. Animal studies (monkey) did not demonstrate this abuse potential.
- Limited available data do not indicate that either psilocybin-naive or experienced individuals will develop dependence after exposure.

Overdosage

- There are no confirmed reports of overdose of pharmaceutical psilocybin.
- In case of accidental overdose, appropriate symptomatic measures should be initiated, followed by monitoring of any adverse events to resolution.

Supply, storage and handling

- A program should be developed to direct the manufacture, licensing, distribution, administration and tracking of psychedelic products. This program should be structured like a pharmaceutical "REMS" program that achieves these defined safety and security objectives in a closed-loop fashion.
- Manufacturer controls should include documentation of drug composition, details of manufacture, stability of the active product, formulation of the final product,

appropriate variation limits, results of analytical testing, specification of the allowable limits of potentially harmful adulterants and packaging.

- Manufacture of psilocybin should also include documentation of the authentication of plant source, record of plant specimens, the history of the land used to grow the plant source, and a written and approved process of the growing process including the use of chemicals on the plant source.
- Manufacturer production requirements should follow Current Good Manufacturing Practices (cGMP). This includes a quality management system, use of high-quality materials, operating procedures, quality monitoring and investigation, laboratory testing, and inspections.
- Manufacturers for products should receive approval / licensing from a state regulatory entity. Maintenance of licensure will require meeting all manufacturer safety standards, reporting requirements, and product manufacture purity, quality, and concentration rules and standards as set forth by the state regulatory entity.
- A tracking system should be created for each product (ie. "Psilocybin Tracking System" and "3,4-Methylenedioxymethamphetamine/MDMA Tracking System"), including unique identification numbers for each lot produced.
- Products must not be produced, transferred or sold as a product appealing to minors.
- All products must be designed to be consumed by a patient orally.
- All products must be maintained in locked areas.
- The manufacturer is responsible for monitoring that pharmacists and clinical providers are adhering to the program requirements. They are also responsible for ensuring that providers meet any training requirements. This includes certification of pharmacies and providers, patient enrollment, training, and monitoring and auditing providers.

Ethical considerations and regulation

The specific recommendations outlined in H.B. 167 addressed by the ethical considerations and regulation workgroup include:

- Any organizations that may provide perspective on ethical considerations
- Any long term societal impacts on use of drug
- Proposed regulations the Legislature should consider in passing legislation that permits the use of psychotherapy drugs to enhance psychotherapy ahead of FDA approval

The workgroup identified a wide array of organizations that provide some perspective on ethical considerations related to drug-assisted psychotherapy, including professional societies that have published codes of ethics, like the American Medical Association, the American Psychiatric Association, and the American Psychological Association, widely-accepted codes of ethics such as the principles in the Belmont Report, and groups that have engaged in research and education about drug-assisted psychotherapy, such as the Multidisciplinary Association for Psychedelic Studies. The workgroup also reviewed legislation relevant to the use of drug-assisted psychotherapy in Utah, such as the Utah Medical Cannabis Act and the Oregon Psilocybin Services Act to identify ethical and regulatory considerations that could be adapted to address the intent of H.B. 167. Finally, the workgroup reviewed a large body of scholarly and academic work that specifically addresses ethical and regulatory issues in the medical use of psychedelic drugs. The findings from these reviews informed the recommendations made below with further detail provided in Appendix I - Ethical and legal considerations of drug-assisted psychotherapy.

The workgroup was asked to consider long term social impacts of drug-assisted psychotherapy and psychedelic drugs generally. It has been speculated that widespread use (not necessarily limited to clinical use) of psychedelic drugs could have both positive and negative social effects. To our knowledge, however, there is little high-quality evidence that addresses this question. It is clear that if drug-assisted psychotherapy is shown to be highly effective for the treatment of certain mental health conditions, it will have a positive social impact in this respect, especially given the limited effect sizes⁴ of many conventional treatments. Importantly, the long term effects of drug-assisted psychotherapy will depend as much on the extent to which these interventions are accessible and the regulations that govern access, as on the intrinsic clinical features of the treatments.

The Ethical Considerations and Regulations workgroup endorses regulations proposed by the other workgroups, and proposes additional regulations informed by our review of ethical and regulatory considerations related to drug-assisted psychotherapy, below.

Recommendations of the Ethics and Regulation Work Group

1. **Psychotherapy Drug Board (PDB) within DHHS:** The Ethics and Regulation Work Group agrees that the Legislature should create a PDB with statutory authority to

⁴ Effect size is a quantitative measure of the magnitude of the experimental effect. The larger the effect size the stronger the relationship between two variables.

review and implement recommendations from the MIPDTF and to recommend regulations to state agencies with authority to regulate psychotherapy drugs as necessary to implement laws passed by the Legislature.

- a. Code of Ethics: The regulatory board should create and publish a code of ethics for the regulation of drug-assisted psychotherapy in Utah.
 - b. Ongoing Review: The PDB should be empowered to conduct an ongoing review of the evidence related to psychotherapy drugs and to recommend amending regulations in light of this review. This could, for example, mean advising DHHS to rescind or revise regulations that permit the use of psychotherapy drugs that are later found to be unhelpful for specific indications, and expanding regulations for psychotherapy drugs that are found to have good evidence for other indications.
2. **Proposed regulations for the Utah Legislature to Consider:** The Utah Cannabis Act (“UCA”) provides a model for laws and regulations that govern the use of a Schedule I product. While many provisions of the UCA could be adopted to apply to drugs used to assist psychotherapy, there are substantial differences between the UCA and the drugs and uses recommended by the Task force. The following are proposed as part of the regulatory framework for drug-assisted psychotherapy:
- a. Immunity from state, administrative, and criminal action for providers and patients who comply with the laws and rules permitting drug-assisted psychotherapy. Providers would still be required to practice in accordance with the applicable standard of care.
 - b. Laws and rules to establish indications for drugs used to assist psychotherapy.
 - c. Regulations for which providers will be permitted to recommend psychotherapy-assisting-drugs and which mental health professionals will be permitted to conduct drug-assisted psychotherapy.
 - d. Regulatory framework for who and which entities will store and dispense psychotherapy assisting drugs. This is likely to include dispensaries or pharmacies as described in the UCA.
 - e. Regulations for assuring the safe manufacturing, storage, transport, and transfer of psychotherapy assisting drugs.
 - f. Regulations that define the process for moving psychotherapy-assisting-drugs from cultivation in the case of psilocybin and ayahuasca and manufacturing in the case of MDMA and LSD to ingestion patients. Unlike cannabis, psychotherapy-assisting-drugs will be ingested in a controlled environment. Unlike cannabis, MDMA and LSD would have to be manufactured from precursor chemicals regulated by the DEA (i.e, List 1 chemicals) that are illegal to possess for manufacturing controlled substances unless authorized by the federal CSA.
 - g. Regulations that set forth training of providers who recommend or engage in drug-assisted psychotherapy.
 - h. Regulations that create an electronic record-keeping system to track the disposition of psychotherapy-assisting-drugs from creation to ingestion.

3. **Patient Safety and Well-Being:** Because of the specific characteristics of drug-assisted psychotherapy, which: (i) may require prolonged contact between patient and therapist; (ii) may be associated with pronounced feelings of intimacy between the patient and therapist; and (iii) may on occasion require physical touch, there is an increased potential for inappropriate contact between therapists and patients in this setting, or for accusations thereof.
 - a. Video Recording: We recommend that providers participating in the act be required to create video recordings, obtained in a fashion that clearly demonstrates all verbal and physical interactions between the therapist(s) and patient, of all patient sessions, *unless* a patient opts out and signs a waiver indicating the desire to opt out; audio recording should be considered if the patient opts out of video recording.. The default should be to create a recording. These recordings should be maintained in a secure fashion, to protect patient confidentiality, for at least two years after each session. In the case that a complaint has been made regarding provider conduct, these recordings should be made available to the regulatory board and/or the licensing board for review.
 - b. Therapist use of psychedelic drugs: Therapists who provide drug-assisted psychotherapy should not be required or permitted to participate in the use of psychotherapy drugs themselves outside of established training programs, either in preparation for providing drug-assisted therapy or via co-ingestion during therapy sessions. Moreover, co-ingestion should be actively prohibited in legislation. Although co-ingestion of psychotherapy drugs by a participant and facilitator is an important part of some shamanistic practices, it is not clearly necessary for the provision of competent and effective drug-assisted psychotherapy, and it increases the risk of boundary violations. If adequate scientific evidence that co-ingestion or therapist training use of psychotherapy drugs improved psychotherapy outcomes in some settings accrues, this guidance could be reconsidered by the regulatory board.
 - c. Enhanced informed consent processes should be utilized prior to drug-assisted psychotherapy. Enhanced consent processes should, in addition to addressing general medical and psychiatric risks associated with psychotherapy drug use, carefully describe the risks that drug-assisted psychotherapy will alter beliefs, cause mystical or spiritual experiences that may be unwelcome, and alter personality. Such consent processes should also address the potential for inducing long-lasting psychotic states. Finally, they should address the potential need for therapeutic touch during the session.
4. **Justice and Equity:**
 - a. Because justice requires fair and equitable access to beneficial medical treatments, provisions should be made to support access to drug-assisted psychotherapy for individuals who are unable to afford associated out-of-pocket fees (for example, encouraging coverage by private insurers for

- approved uses, providing state subsidies for drug-assisted psychotherapy, or including coverage for drug-assisted psychotherapy in state Medicaid guidelines)
- b. Regulatory mechanisms should permit and encourage the adoption of novel therapy approaches that could reduce the costs of drug-assisted psychotherapy or expand access to them if accruing scientific evidence supports their efficacy.
 - c. Compassionate Use: The legislature should consider permitting the compassionate or palliative use of drug-assisted psychotherapy for persons who have severe and treatment-refractory symptoms, whether these are due to a physical illness, a mental illness, or represent existential distress related to incurable cancer, neurologic disorders such as amyotrophic lateral sclerosis, or other severely disabling and life-limiting conditions. Although the evidence base supporting use in such conditions may be very limited, the utilization of treatments that have some promise of benefit in conditions that cause severe suffering and which have not responded to all standard treatments is generally regarded as ethically permissible, and indeed may be an ethical obligation for appropriately trained providers.
5. **Mitigation of inherent violations of federal laws including the federal Controlled Substances Act:** The possession, distribution, and manufacturing of the substances being considered by the Task Force is unlawful under the federal CSA and carry criminal penalties. While the federal government has passed a law that prevents the use of Department of Justice funds for interfering with states' implementation of medical marijuana laws, no such protection exists for the Schedule I substances being considered by the Task Force. Utah should evaluate the most effective means to mitigate the risks of federal prosecution, including: (i) communicating with U.S. Attorney's office to discuss local enforcement of the CSA; (ii) reaching out to Department of Justice officials to seek enforcement memoranda similar to the Ogden and Cole Memoranda⁵ that apply to drugs to assist with psychotherapy; and (iii) working with Utah's congressional members and other congressional leaders to draft legislation that allows the use of certain schedule I substances to assist with psychotherapy.

Conclusions and recommendations for next steps

A comprehensive review of the peer-reviewed scientific literature finds that MDMA and psilocybin are the 2 schedule I controlled substances with a growing body of evidence

⁵ See [DOJ "Ogden Memorandum" Oct. 19, 2009](#); ["Cole Memorandum" June 29, 2011](#); ["Cole II Memorandum" Aug. 29, 2013](#).

supporting their efficacy and safety as medication adjuncts to facilitate manualized psychotherapy for specific disorders (PTSD for MDMA and treatment resistant major depressive disorder and end of life related anxiety and depressive symptoms for psilocybin). Both substances are under fast-track review by the FDA and sources indicate that we may see FDA approval for MDMA assisted-psychotherapy for the treatment of PTSD as soon as the end of 2023. In light of emerging promising evidence and ongoing fast-track reviews of MDMA and psilocybin by the FDA, the MIPDTF recommends Utah not proceed with the creation of any psychedelic-assisted psychotherapy program ahead of FDA approval. This is the most conservative course of action to ensure the safety of citizens of Utah while minimizing regulatory burdens and cost.

If the Legislature decides to move ahead prior to FDA rulings on MDMA and psilocybin, then the extensive guidance described in the body of this report should be followed to ensure the safety of the people of Utah. In addition, the MIPDTF recommends two additional areas requiring further study prior to enacting any legislation:

1. A fiscal analysis of the one-time and the ongoing costs of developing a statewide program overseeing psychedelic-assisted psychotherapy to the taxpayers of Utah; and
2. An evaluation of the most appropriate framework for risk evaluation and mitigation to ensure the benefits of psychedelic-assisted psychotherapy outweigh its risks and what governmental entity in Utah should be responsible for managing this part of the regulatory framework.

The task force has completed the scope of work outlined in H.B. 167 and could sunset ahead of the January 1, 2024 date outlined in statute. It would be appropriate to continue to monitor the status of the FDA approval of any psychedelic drugs used to assist psychotherapy should occur to reassess new developments in the evidence that might influence the task force's current recommendations. Based on the comprehensive nature of the evidence review conducted for this report, no additional evidence review for other schedule I controlled substances is recommended at this time.

Appendix A - Task force members and qualifications

The current members of MIPDTF and their qualifications include:

Mark Rapaport MD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Mark Rapaport is chief executive officer of the HMHI, William H. and Edna D. Stimson Presidential Endowed Chair, and Professor and Chair, for the University of Utah Department of Psychiatry and serving as co-chair of the MIPDTF. Serving as co-chair for the MIPDTF, Dr. Rapaport brings a long history of peer-reviewed funding from NIMH, NCCIH, VA, BBRF, and other sources. He has expertise in clinical trial design and methodology and he has run a training program for New Investigators in the field since 1992. He has served and chaired review committees for NIDA and started the DSMB for the NIDA clinical trials network.

Michelle Hofmann MD, MPH, MHCDS

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Michelle Hofmann is executive medical director of DHHS and serving as co-chair of the MIPDTF as the executive director's designee. Dr. Hofmann is Associate Professor of Pediatrics at the University of Utah School of Medicine and has been a faculty member since 2004. Dr. Hofmann currently serves as the deputy director of the DHHS Clinical Services Section, which includes the Center for Medical Cannabis, the Office of the Medical Examiner, the Utah Public Health Laboratory, the Office of Primary Care and Rural Health, the Health Clinics of Utah, and the Office of Health Equity.

Benjamin Lewis MD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Benjamin Lewis is Assistant Professor of Psychiatry at the HMHI and serving in the licensed psychiatrist position on the MIPDTF. Dr. Lewis has been a faculty member at the University of Utah for 10 years with expertise in adult psychiatry and psychopharmacology. He is currently engaged in clinical research on psychedelic-assisted therapies with

psilocybin and ketamine and is the medical director of the HMHI Ketamine-Assisted Psychotherapy Clinic. He has completed training in psychedelic medicine through the California Institute of Integral Studies Certificate Program in Psychedelic Therapy and Research, the Multidisciplinary Association of Psychedelic Studies (MAPS) certification in MDMA-Assisted Therapy for PTSD, and the Psychedelic Research and Training Institute (PRATI) training program in ketamine-assisted psychotherapy.

Nanci Klein PhD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Nanci Klein is serving in the licensed psychologist position on the MIPDTF. Dr. Klein is the Director of Professional Affairs for the Utah Psychological Association. In this capacity she has managed Psychology's agenda at the Utah State Legislature for the past 25 years. Dr. Klein has worked in the mental health field since 1973, and has maintained a private out-patient psychotherapy practice in Salt Lake City, Utah since 1986, having co-founded the Utah Institute for Psychotherapy and Training. She has adjunct appointments to the University of Utah Department of Psychology and Department of Psychiatry. Dr. Klein has served on numerous national committees dealing with behavioral health practice issues, including serving as the only psychologist on the AMA CPT Psychotherapy Revision Work Group. In addition to her private practice and Director of Professional Affairs work, Dr. Klein also provides ongoing consultation to the American Psychological Association regarding professional psychology scope of practice and regulation.

Jennifer Strohecker PharmD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Jennifer Strohecker is the Director, Division of Integrated Healthcare and State Medicaid Director and is serving in the licensed pharmacist position on the MIPDTF. Dr. Strohecker brings more than 20 years of clinical and administrative pharmacy experience to this role from a variety of settings, including inpatient hospital, ambulatory medicine and managed care settings. Dr. Strohecker has served as the State Pharmacy Director for 4 years and was appointed as the State Medicaid Director / Director, Division of Integrated Healthcare 9 months ago.

Aaron Vazquez MD, MBA

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Aaron Vazquez is serving as a representative of the Utah Medical Association on the MIPDTF. He is the Medical Director for Behavioral Health at St George Regional Hospital - Intermountain Healthcare; where he works as an inpatient psychiatrist. Dr. Vazquez has worked as a consultant in Southern Utah to assist outpatient mental health clinics integrate ketamine-assisted psychotherapy into their current practice models. Aaron has an interest in caring for patients that are deemed “treatment-resistant” to conventional treatment. He is board certified by the American Board of Psychiatry and Neurology and teaches medical students as an Adjunct Clinical Associate Professor at Rocky Vista University College of Osteopathic Medicine. He completed his Adult Psychiatry Residency at University Hospitals of Cleveland/Case Western Reserve University and served as the Clinical Chief Resident. He graduated with a Bachelor of Science degree in Psychology from Brigham Young University and was a clinical researcher at the Cleveland Clinic, and Center for Change.

Pam Bennett LCSW, PhD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Bennett is a Program Administrator III in the Office of Substance Use and Mental Health and is serving as the individual who researches and studies neuroscience and mental health on the MIPDTF. Dr. Bennett has worked as an Assistant Research Professor for the University of Utah Department of Psychiatry and as a Research Biologist at the George E Wahlen Veteran Affairs Medical Center in Salt Lake City. Research has focused on the molecular genetics of psychiatric illnesses. Dr. Bennett has clinical experience as an LCSW working at a rural local mental health authority, and currently provides administrative oversight for multiple adult mental health programs.

Mason Turner MD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Turner has been board certified in Psychiatry by the American Board of Psychiatry and Neurology since 2004 and in Addiction Medicine by the American Board of Preventive Medicine since 2017. He is serving on the MIPDTF as the representative from a Utah hospital or a major healthcare system. He is a fellow of the American Society of Addiction Medicine and is a member of both the Utah and California Societies of Addiction Medicine.

He has served in leadership positions with the California Society of Addiction Medicine for the last 16 years, including most recently as Chair of the Education Committee. He is also a member of the American Psychiatric Association and the Academy of Consult-Liaison Psychiatry.

As the Director of Outpatient Mental Health and Addiction Medicine for Kaiser Permanente Northern California for 10 years, he sponsored the creation of their first ketamine treatment program for depression in 2014, which has now treated hundreds of patients. For the last year, he has served as Senior Medical Director for Behavioral Health at Intermountain Healthcare, headquartered in Salt Lake City. He currently treats patients in the Access Center at LDS Hospital in Salt Lake City.

Kylee Shumway PharmD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Dr. Kylee Shumway has a Doctorate of Pharmacy from Roseman University of Health Sciences with 6+ years of clinical experience specializing in bio-identical hormone replacement therapy, compounding. Current Director of Medical Research and Advocacy for WholesomCo Cannabis where she leads educational efforts in the community and with Utah patients. Current Medical Director for the Utah Patients Coalition. Dr. Shumway is serving on the MIPDTF as the patient who is knowledgeable about the use of a psychotherapy drug and nominated by a patient advocacy group.

Jeremy Christensen, LCSW

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Jeremy Christensen is the Assistant Superintendent and Forensic Director at the Utah State Hospital and serving on the MIPDTF as a trauma focused therapist. He is a licensed Clinical Social Worker providing mental health care both publically and in private practice for over 24 years and served as Assistant Director at the Utah Division of Substance Abuse and Mental Health, Department of Human Services from 2013-2019 with oversight of mental health programming including crisis care, suicide prevention and trauma focused services. Jeremy has served on multiple boards and committees covering a range of subjects, including domestic violence, sexual abuse, evidence-based practice, forensic services, peer support, suicide prevention, homelessness, deaf and hard of hearing, and diversity.

William Stilling, B.S. Pharm., M.S., JD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

William Stilling is an attorney and licensed pharmacist. He is a partner at Stilling & Harrison, PLLC, a firm that focuses on healthcare law, and previously chaired the healthcare practice group at Parsons Behle & Latimer. Mr. Stilling advises individual health care providers and healthcare entities about, among other things, legal issues related to pharmaceuticals and controlled substances. For some twenty years, Mr. Stilling taught the pharmacy law course at the University of Utah College of Pharmacy, which included federal and state laws governing controlled substances. He has lectured to national and local groups about how to reduce the diversion of controlled substances from pharmacies and health care entities, recent cases and regulatory developments in pharmacy and controlled substances laws, and about the interface of state laws allowing the use of cannabis and the federal laws prohibiting such use. Mr. Stilling is past president of the American Society for Pharmacy Law and an adjunct associate professor at the University of Utah College of Pharmacy where he continues to lecture on drug law. He is serving on the MIPDTF as a licensed attorney with knowledge of controlled substance law. licensed attorney with knowledge of controlled substance law.

Brent Kious, MD, PhD

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Qualifications: Dr. Brent Kious is Assistant Professor of Psychiatry at the HMHI, and an Adjunct Professor in the Departments of Internal Medicine (Medical Ethics) and Philosophy at the University of Utah. He is serving on the MIPDTF as a medical or psychiatric ethicist with knowledge of the ethical and legal issues pertaining to psychotherapy drugs. Dr. Kious is a licensed psychiatrist with expertise related to adult psychiatry and clinical research. His research focuses on ethical issues in psychiatry.

Elizabeth Howell, MD, MS

Disclosure: No financial ties to industry or pharmaceutical companies related to substances or treatments reviewed in this committee.

Elizabeth F Howell, MD, MS is Professor of Psychiatry (Clinical) at the University of Utah School of Medicine and has an adjunct appointment in the Division of Epidemiology, Department of Internal Medicine. She is serving on the MIPDTF as the clinician board certified in addiction medicine She has an inpatient and outpatient clinical practice at the

HMHI and University of Utah Health. She is Board certified in Psychiatry and Addiction Psychiatry by the American Board of Psychiatry and Neurology, and in Addiction Medicine by the American Board of Preventive Medicine. She developed and is training director for the Addiction Psychiatry and Addiction Medicine ACGME-accredited fellowship programs at the University of Utah School of Medicine.

Appendix B - Task force workgroups

Indications and Prescribing Practices

Benjamin Lewis, MD

Nanci Klein, PhD

Mason Turner, MD

Kylee Shumway, PharmD

Elizabeth Howell, MD

Pamela Bennett, LCSW, PhD

Licensure and Training Needs

Jeremy Christensen, LCSW

William Stilling, JD

Mason Turner, MD

Michelle Hofmann, MD, MPH, MHCDS

Patient Safety

Jennifer Strohecker, PharmD

Kylee Shumway, PharmD

Elizabeth Howell, MD

Pamela Bennett, LCSW, PhD

Ethical Considerations and Regulation

William Stilling, JD

Brent Kious, MD, PhD

Michelle Hofmann, MD, MPH, MHCDS

Aaron Vazquez, MD

Jeremy Christensen, LCSW

Appendix C - Record of attendance

[May 31, 2022 Meeting](#)

[June 14, 2022 Meeting](#)

[July 12, 2022 Meeting](#)

[August 16, 2022 Meeting](#)

[September 13 2022 Meeting](#)

May 31, 2022 Meeting

Task force members present:

Dr. Mark Rapaport

Tracy Gruber

Dr. Michelle Hofmann

Dr. Pam Bennett

Dr. Nanci Klein

Dr. Kylee Shumway

Dr. Benjamin Lewis

Dr. Brent Kious

Dr. Mason Turner

Dr. Jennifer Strohecker

Jeremy Christensen

Dr. Elizabeth Howell

William Stilling

Others Present:

Pete Caldwell

Marc Watterson

Ross Van Vranken

Dr. Lauren Heath

Tony Patterson

Joanne LaFleur

[October 4, 2022 Meeting](#)

[October 18 2022 Meeting](#)

[October 27, 2022 Meeting](#)

[October 31, 2022 Meeting](#)

June 14, 2022 Meeting

Task force members present:

Dr. Mark Rapaport

Dr. Michelle Hofmann

Dr. Pam Bennett

Dr. Nanci Klein

Dr. Kylee Shumway

Dr. Benjamin Lewis

Dr. Brent Kious

Dr. Mason Turner

Jeremy Christensen

Dr. Elizabeth Howell

William Stilling

Others present:

Pete Caldwell

Mollie McDonald

Kevin Byrne

Monet Luloh

Dr. Lauren Heath

Nataunya Kay

Ross Van Vranken

Reid Robison

Miriam Barth

Molly Davis

Joanne LaFleur

Kylee Ford

Connor Boyack

July 12, 2022 Meeting

Task force members present:

Dr. Mark Rapaport
Dr. Michelle Hofmann
Dr. Pam Bennett
Dr. Nanci Klein
Dr. Kylee Shumway
Dr. Benjamin Lewis
Dr. Brent Kious
Dr. Mason Turner
Dr. Jennifer Strohecker
Jeremy Christensen
Dr. Elizabeth Howell
William Stilling

Others present:

Kimberlie Raymond
Monet Luloh
Ross Van Vranken
Chris
Amy Pomeroy
Connor Boyack
Dr. Lauren Heath
Loanne LaFleur
Sujin Lee

August 16, 2022 Meeting

Task force members present:

Dr. Mark Rapaport
Dr. Michelle Hofmann
Dr. Pam Bennett
Dr. Nanci Klein
Dr. Kylee Shumway
Dr. Benjamin Lewis
Dr. Brent Kious
Dr. Mason Turner
Dr. Jennifer Strohecker
Jeremy Christensen
Dr. Elizabeth Howell
William Stilling
Dr. Aaron Vazquez

Others present:

Pete Caldwell
Nancy Huntsman
KN
Dez
Zane Jordan
Monet Luloh
Dr. Lauren Heath
Kevin Byrne
Dr. Michelle Nixon
Connor Boyack
Amy
Kylee Ford
Reid Robison
Amanda Stoeckel

September 13, 2022 Meeting

Task force members present:

Dr. Mark Rapaport
Dr. Michelle Hofmann
Dr. Nanci Klein
Dr. Brent Kious
Jeremy Christensen
Dr. Benjamin Lewis
Dr. Jennifer Strohecker
William Stilling
Dr. Aaron Vazquez
Dr. Kylee Shumway
Dr. Elizabeth Howell
Dr. Mason Turner
Others present:
Pete Caldwell
Dr. Lauren Heath
Desiree Hennessy
Connor Boyack
Monet Luloh
Amy Pomeroy
Ross Van Vranken

October 4, 2022 Meeting

Task force members present:

Dr. Mark Rapaport
Dr. Michelle Hofmann
Dr. Pam Bennett
Dr. Nanci Klein
Dr. Benjamin Lewis
Dr. Brent Kious
Dr. Jennifer Strohecker
Jeremy Christensen
Dr. Elizabeth Howell

Others present:

Pete Caldwell
Dr. Lauren Heath
Valerie Gonzales
Desiree Hennessy
Ross Van Vranken
Monet Luloh
Joanne LaFleur
Connor Boyack
Zoom user

October 18, 2022 Meeting

Task force members present:

Dr. Mark Rapaport
Dr. Michelle Hofmann
Dr. Kylee Shumway
Dr. Jennifer Strohecker
Dr. Benjamin Lewis
Dr. Mason Turner
Dr. Brent Kious
William Stilling
Jeremy Christensen
Dr. Elizabeth Howell
Dr. Aaron Vazquez
Dr. Pam Bennett
Dr. Nanci Dlein

Others present:

Dr. Lauren Heath
Pete Caldwell
Mollie McDonald
Monet Luloh
Connor Boyack
Valerie Gonzales
Amy

October 27, 2022 Meeting

Task force members present:

Dr. Mark Rapaport
Tracy Gruber
Dr. Nanci Klein
Bill Stilling
Dr. Benjamin Lewis
Dr. Mason Turner
Jeremy Christensen
Dr. Kylee Shumway
Dr. Jennifer Strohecker
Dr. Elizabeth Howell
Dr. Aaron Vazquez

Others present:

Pete Caldwell
Molly Davis
Connor Boyack

October 31, 2022 Meeting

Task force members present:

Dr. Mark Rapaport
Tracy Gruber
Bill Stilling
Dr. Pamela Bennett
Dr. Brent Kious
Dr. Benjamin Lewis
Dr. Nanci Klein

Dr. Jennifer Strohecker

Dr. Elizabeth Howell

Dr. Mason Turner

Jeremy Christensen

Others present:

Pete Caldwell

Marc Watterson

Rebecca Brown

Desiree Hennessy

Appendix D - Summary of public comments

Since the June 14, 2022 meeting, all postings on the Utah Public Notice website have included four questions for the public to respond to should they wish. The questions are:

1. Based on legislative intent and the planned review of the current state of the evidence, what are the most important questions for us to ask to inform our recommendations to the Legislature by October 31, 2022?
2. What concerns are there related to the safe use of psychedelic drugs to enhance psychotherapy when treating a mental illness?
3. What are the best indications for the use of psychedelic drugs to enhance psychotherapy when treating a mental illness and why?
4. What ethical considerations are necessary to allow the field of psychedelic research to grow in a safe and sustainable manner?

[Comments from May 31, 2022 Meeting](#)

[Comments from June 14, 2022 Meeting](#)

[Comments from July 12, 2022 Meeting](#)

[Comments from August 16, 2022 Meeting](#)

[Comments from September 13 2022 Meeting](#)

[Comments from October 4, 2022 Meeting](#)

[Comments from October 18 2022 Meeting](#)

[Comments from October 27, 2022 Meeting](#)

[Comments from October 31, 2022 Meeting](#)

Comments from May 31, 2022 Meeting

No public comment was offered.

Comments from June 14, 2022 Meeting

Connor Boyack: Great to be with you, my name is Connor Boyack, I'm the president of Libertas Institute. We're the non-profit that helped draft the bill that created your group. It's been fun to join you today and clearly there's a bunch of really smart people on the task force and I'm really excited about what I'm hearing. I wanted to respond to two questions that came up in case it's any help. I can't really see any names so I apologize, I think it was Ben that asked about legalization, I would point the task force to if you have access to the bill, line 109, it's actually the last parameter that we put in. It was intended to be intentional for the task force to give additional input, it says that one of the items to respond to is any proposed regulation the legislature should consider if the psychotherapy drug is made legal for treating mental illness. We did not contemplate, the legislature is not going to support decriminalization, we do not want the task force to be looking into or planning on that. This is a legalization route, but that is the catch all where if the task force has any feelings on anything pertaining to how it should be done, where it should be grown, how should it be stored, that's the catchall that we put there. Dr. Rapaport mentioned CMS and eight hours and therapy and everything. We envision this going to happen much like medical cannabis which is to mean outside of the system. We don't think any insurance providers are going to be covering this or Medicare or anything like that. And to that end what I really want to leave this committee with is our organization, and myself in particular, played a lead role in drafting and pushing for the medical cannabis law, what I can offer to anyone on the task force informally if you would like to chat at any point is a lot of institutional knowledge on how we crafted those regulations, how they started, how they ended, how we went through the whole process, what we learned, what would be helpful in terms of replicating or carrying any of that forward into this model. I think what a lot of folks were talking about on the call today, in particular there's going to be a lot more certainty in terms of what the studies are saying, but when you get into the legal and regulatory then the studies aren't going to be fully informative, how the programs should be designed. So if I could be useful at all, I'd be happy to. I'll leave my card with Pete and he can send my contact info out in case that's helpful for anyone. I'm really excited about what we're hearing and appreciate you guys spending the time on the task force. Thanks.

Comments from July 12, 2022 Meeting

Connor Boyack: I suppose if I am limited to the one, it would be first. In terms how this Task Force is going to make its ultimate recommendation. For clarity, and reminding folks. I run the Libertas Institute, and we were involved with legislation that created your Task Force. I

have an interest and have seen the results, and what comes from it. I am glad to see the Task Force decide on that Option 2. Someone mentioned, maybe the Task Force could comment on drugs that were not narrowly searching to educate the public or discuss things. I think ultimately legislator would be looking for, certainly the public. Is your informed perspective on things that may not have not gone into depth on your report. Because inevitably if the Task Force goes narrow and deep towards the drugs disease pairs mentioned. There is obviously be interest in how Psilocybin for anxiety, and some of these other things. Having additional commentary in the ultimate report to the extent that the Task Force feels comfortable doing this. Or if there is enough research behind it to say, look even if we didn't go deep over here. As for an example Psilocybin for anxiety, we believe based on x, y, and z that the legislator might consider this. Or things like that may be immensely useful. If there is an openness to that.

The second comment then would be, I believe the Task Force primary audience is the legislator not the public. Someone mentioned earlier maybe we can educate the public in harm reduction. I value and agree with all those things, but ultimately I believe your audience is back to the legislator. So I don't know if the Task Force current role is to a lot of public education at least as of now. I think the goal is a lot of legislators have no clue about any of this stuff. We got them to agree to create you Task Force to then inform them. But I think we need to keep in mind ultimately there the primary focus and audience.

Finally, what I'll to say is I agree with the person that said: This is an interesting and daunting task. Our organization was the group behind the medical cannabis push. Myself, I was involved crafting the policy negotiating with all the stakeholders. And ending up with what we have today. When you're trying to create a state regime to legalize a federally illegal substance. It is interesting and daunting. But we have done it before, we figured it out and now tens of thousands of people have had help. So as with last month, I'll offer myself, if any of you want to chat offline. Your sub-group would be interested in what we learned, and went through. And how we landed where we did. In light of some of these consideration that are very similar when it comes to these drugs, I am happy to chat. Because as you look to other states for the legal programs there is a very stark difference decriminalization. And an active legal program with regulations around growing this, storying it, dispensing it, recommending it, and providing it to patients through this therapy process. I will leave my email, and cell phone in the chat if it is an interest to anyone. Again I am happy to offer my experience, and insights we gained, if it is useful to you in your work. Thank you.

Comments from August 16, 2022 Meeting

Kylee Ford: (I thought I needed to send in the form to attend) I will say to Dr. Rappoport point of having justice in having well trained guides. I would just say that I work in the hospital, and I am seeing patients come into the hospital with experiences of underground sessions that are currently happening in Utah. With guides with no training, and there are a lot of boundary violations that are happening anecdotally. I second everything that is being said there.

Kimberly Nielsen: I do not have a comment, I just filled out the form just in case I did. I am a licensed mental health therapist. And I'm doing training on psychedelic drugs. Thank you very much.

Kevin Byrne: I am a fourth-year adult psychiatry resident, and chief resident at the University of Utah. Psychiatry needs additional tools, so I am really excited by the research looking into psilocybin assisted psychotherapy for depression. And MDMA assisted psychotherapy for PTSD. The biggest and most important concerns I have. Is treatment and how they are potentially rolled out as we move forward with the research is safety. I want to reiterate and celebrate some of the remarkable safety results that Dr. Lewis presented earlier in this meeting. What you talked about was essentially studies have demonstrated a remarkable safety. And for both of these treatments modalities when utilized in a therapeutic container. With robust support in place with appropriate participants population.

I also wanted to mention I am excited by the early results regarding the effect size for some of these treatments. Which would suggest that they may become useful for therapeutic tools. And in some cases, this may even rival the efficacy in some of our current standards of care. Although this is yet to be seen.

Lately I wanted to mention I have had the personal privilege as acting as a therapist in a psilocybin assisted psychotherapy trial. During my time in residencies, titled A Pilot Study of Psilocybin Enhanced Group Psychotherapy and Patients with Cancer, also known as the hope trial. This took place at the Huntsman Cancer Institute. In this trial I was very impressed by the safety and the robustness of the manner in which the psilocybin assisted psychotherapy was administered in the study. I got a glimpse of the powerful therapeutic potential of this treatment. I appreciate the work that everyone is doing to explore the evidence around these drugs. Thank you.

Comments from September 13, 2022 Meeting

Connor Boyack: It has been really good information; I appreciate everyone's hard work on this. 2 quick points of feedback. As we were talking about which indications one of the lessons, we have learned from the medical cannabis work. Is there is over recommendation you might say for pain. Because people are using it for other indications not specifically enumerated in state law. And as such the recommending providers are saying, well, that sounds like pain to me. Or patients are self-labeling as if saying, hey, this is pain, therefore I qualify. One of the concerns is if we niche down to specific conditions or indications for something like psilocybin for example. Then other potential indications wither it is the alcohol use disorder or anxiety or something like that. People are practically suffering from overly unnecessary lumped into major depressive disorder. If there was a more open way to say here are these indications for which we think there is strong evidence. The other might have less evidence, that the task force thinks, given there is no addition here or no overdose.

Maybe there is a two-tier approach. Indications for which has a significant amount of evidence maybe there is a more laxed clinical oversight regulatory kind of process. Whereas you are using it for these other indications we still want to collect that data. We still recognize people are still going to use it. But let's try and get the proper indications, maybe we can get good data out of that. That can be informative for the research. It is something to think about if we go too restive and narrow, we potentially recreate that problems we see in medical cannabis. Then the data get fuzzy because everyone in pain, and some that be insomnia, because we don't track the data that way. It becomes harder to get something helpful out of it.

Second point, on the medical cannabis side the number of hours for which a provider has to go through training. To become what's, called a qualified medical provider or what you are referring to a certified medical provider is four hours. The draft recommendation (I don't remember what group was sharing that) said 180 to 120 hours. Whereas someone was expression the concerns about cost for low-income people. What we have very clearly seen on the medical cannabis side is that the small number of physicians recommending this. And doing it for their patients has bottled neck the program into a small number of providers who charge more. If one goal is to lower cost in a more distributed opportunity for people to work with their mental health practitioner and clinicians. I would encourage that task force to really think seriously about how much certification is going to be required. Because if you create barriers to entry for clinicians to become certified you are

going to have a very small number. Who then as a result of their small numbers can charge much higher prices for their services. That is also something we have seen.

The legislator in the year since we passed Prop 2 have actually walked back the number of regulations needed. We now have limited providers; you don't have to get any training at all. You can have a certain number of patients before even being obligated to get the certification. I believe once you hit 15 patients then you have to do the 4 hours and pay the fee. Because legislator say at the point you are interested enough, and you are doing this for enough patients you can go through the process. They have been actually decreasing the certification standard for medical cannabis. I would love to have the task force to learn from that kind of challenge we had on that side as well. Where the cost was ballooning as the patient population was spread – concentrated on a very kind of small provider population. I hope that is helpful, thank you for letting me comment.

Comments from October 4, 2022 Meeting

Connor Boyack: Question about compassionate use. When the medical cannabis act there was a recognition among stakeholders that part of the challenge of figuring out the regulation is that a lot of people were using cannabis anyways and if we create a creative to tighter regulatory framework we would be keeping a lot of patients in kinda this criminal status they be out on the black market getting product that wasn't regulated we wouldn't be obtaining the data to better understand who's benefiting from this and how so I like the discussion around compassionate use and out of that recognition that a lot of patients might be using this anyways if they don't qualify for psilocybin for you know some type of severe anxiety even if it isn't a kind of terminal illness anxiety having a compassionate use path I think it's going to be important. On a cannabis sight it is this more significant robust review of the patients seeking a permission its multiple physicians reviewing this on the board coming together to say in these circumstances does this make sense are we OK with this before that individual is able to do it so just having that stop valve for some of these patients who are in a desperate circumstance are they tried everything else rather than saying no out right having an option for them where there's perhaps more scrutiny more oversight more of a hurdle but still that option to prestige both allows those patients to come out of the criminal status and get the protections they need legally but it also ensures they're using quality product through a medical provider and not some random person on the street guiding them through the process but then also we as you know the public policy makers stakeholders everyone else can gather that data and better learn about who's actually benefiting from this and how so. I just want to call that out that I think compassion is process is going to be important to preserve it as we do so we should frame that around

like you know let's just have those extra precautions and stats just to make sure we're very careful about who gets through who might be able to get permission.

Comments from October 18, 2022 Meeting

No public comment was provided.

Comments from October 27, 2022 Meeting

Connor Boyack: Hey, guys Connor Boyack from Libertas Institute. Thanks for all your hard work. I just want to briefly register a concern. Just so it's on the record more than anything. Taking a vote on a document that hasn't been finalized is somewhat like asking legislators to vote on a proposed bill that they haven't seen the final version of. I do think it's a little concerning to leave it in the hands of others to come up with final language, that others have preemptively approved, I totally recognize the time constraints, and all of that. However, with that being said, depending on the outcome it will be interesting to see if the task force members are all of a like mind on how the language ended up. It just is a little bit procedurally odd to take a final recommending vote on something that has not yet been finalized. So again, circumstances are what they are but just wanted to make sure that, that comment was left for the record.

Comments from October 31, 2022 Meeting

No public comment was provided.

Appendix E - Evidence review description of methods

Phase I rapid evidence review

- Used guidance from the World Health Organization for rapid reviews,¹ and Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)² to define a research question, specify criteria for inclusion in the review, and conduct a literature search.
 - The research question and literature search targeted certain controlled substance: mental health condition pairs (see Table). MIPDTF members were asked to suggest additional records for screening.
 - Title and abstract records from the literature search were screened independently and in duplicate using the eligibility criteria listed below.
 - Full text records identified from title/abstract screening were screened for inclusion in the annotated bibliography by a single DRRC member, with consultation with others as needed.
- Eligibility criteria for the annotated bibliography were: (1) Population and studied intervention(s) were one of the controlled substance-disease pairs listed in Table 1; (2) study design was an experimental trial, long-term follow-up of an experimental trial, summary study (ie, including 2 or more experimental trials) conducted by the same sponsor that included trials not published as an individual report, or secondary (eg, post-hoc or exploratory) analysis of an experimental trial of any length; (3) for experimental trials, must have included a comparator group of any type; and (4) was published in the year 2010 or later.

Schedule I Controlled Substance ^a	Mental Health Condition(s) ^{a,b}
MDMA	1. PTSD 2. Anxiety
LSD	1. Anxiety 2. Depression
Psilocybin	1. Anxiety 2. Depression 3. Demoralization associated with chronic illness 4. PTSD 5. Substance Use Disorder
Ayahuasca (or DMT)	1. Depression
Ibogaine	1. Substance Use Disorder

Abbreviations: DMT, *N,N*-dimethyltryptamine; LSD, lysergic acid diethylamide; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder;

^a The literature search also contained synonyms or related terms for each drug and disease

^b Although these specific conditions were used to narrow the search results, trials for other mental health conditions were considered for inclusion for each controlled substance if found among the results.

The Phase I review included 43 records that were summarized in an annotated bibliography. Most of the records were for MDMA (n=18, 41.9%) or psilocybin (n=16, 37.2%). Records were also found for LSD (n=3, 7%), ayahuasca (n=5, 11.6%) and ibogaine (n=1, 2.3%). MDMA-assisted therapy for the treatment of PTSD was the controlled substance: mental health condition pair furthest along in clinical development, with at least 1 completed phase 3 randomized controlled trial and multiple phase 2 trials. The controlled substance: mental health condition pair next furthest along in clinical development was psilocybin-assisted therapy for the treatment of depression. Three phase 2 trials evaluated psilocybin-assisted therapy for the treatment of major depressive disorder, and 3 additional smaller trials evaluated psilocybin for the treatment of cancer-associated anxiety, depression or psychological distress. See Appendix F for the Annotated Bibliography.

Phase II rapid evidence review

Although the MIPDTF was given a broad scope, the decision was made to focus on MDMA and Psilocybin due to the amount of research conducted compared to the other drugs considered.

- Used similar methods as Phase I to expand the literature search to 2 additional databases, and screen the results for experimental trials meeting the eligibility criteria listed below.
- Eligibility criteria for Phase II were:
 - P/I: MDMA for PTSD, or psilocybin for depression (\pm other interventions such as psychotherapy as long as it was delivered equally to all study groups including the control)

§ Trials including a heterogeneous mental health population (e.g., people diagnosed with anxiety with or without depression) that did not report results among the target mental health condition specifically (e.g., only depression) were excluded.

- C: control (any type)
- O: includes one or more of the following:
 - § Efficacy: change in disease-specific outcome measure (e.g., CAPS total score for PTSD)
 - § Safety: hospitalizations, death, treatment-emergent psychiatric events
- T: published, registered, or presented from 2010-present
- S: experimental trials, or summary studies of experimental trials conducted by the sponsor of the trials that reported findings not found in individual trial reports
- Published with sufficient detail to verify meeting inclusion criteria (e.g., published as an abstract only).

- The Phase II data extraction included selected patient characteristics, study design and setting including details about the therapy regimen and information about therapists/facilitators, efficacy and safety results, and a risk of bias assessment. Data extraction focused on outcome data from double-blinded study periods with a control group. Information was summarized as a qualitative evidence synthesis.
- The risk of bias assessment used the domain-based approach by Page et al.³ This addressed major bias threats to randomized controlled trials including those arising from randomization, allocation concealment, blinding (of participants, personnel and outcome assessors) and incomplete outcomes. These domains are assigned a level of bias risk (ie, low, unclear, or high) based on pre-specified criteria. Based on discussion with the MIPTF, the domain-based bias assessment was supplemented with additional assessment of selective reporting of outcomes (i.e., discrepancies between different reporting sources for the same trial if available), adherence to study interventions, fidelity of therapists to the psychotherapeutic approach, and funding bias. Finally, a JADAD score was calculated.⁴

Phase II rapid evidence summary included 11 MDMA studies (8 randomized controlled trials,⁵⁻¹² and 3 summary studies¹³⁻¹⁵ that included subsets of those trials), and 3 psilocybin trials.¹⁶⁻¹⁸ The 8 (one phase 3 trial and 7 phase 2 trials) MDMA-assisted therapy for moderate-severe PTSD trials were small studies, with the phase 2 trials ranging from 5-28 enrolled participants⁶⁻¹² and the largest being the phase 3 trial with 91 participants.⁵ The psilocybin-assisted therapy for depression randomized controlled trials included 2 trials among people with moderate-severe major depressive disorder (ranging in size from 27-59 participants),^{16,18} and 1 trial among people with treatment-resistant major depression (233 participants).¹⁷ See Appendix G for a full summary of results from the Phase II evidence review.

Appendix F - Annotated bibliography

MDMA Studies

MDMA for PTSD

Citations addressing the original phase 3 trial by Mitchell et al. 2021 (NCT03537014)

1. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med.* 2021;27(6):1025-1033.

P: Adults (mean age of 41 years, 65.6% female at birth) with severe (Clinician-Administered PTSD Scale [CAPS]-5 total score ≥ 35 ; mean score of 44.1 at baseline) PTSD. Other psychiatric medications were discontinued before baseline (total n randomized = 91)

I: MDMA (80-180 mg in divided doses [first dose at start of treatment session, plus half-dose 1.5 to 2.5 hours later] *three times*, during treatment sessions) plus “manualized” therapy by trained therapists with a master’s or higher degree (3, 90-minute ‘preparatory’ sessions pre-treatment plus 3, 8-hour treatment sessions, separated by ~4 weeks plus 3, 90-minute integration’ sessions following each treatment session and separated by about 1 week)

C: Inert placebo in divided doses with “manualized” therapy, both as per the MDMA arm

O: Change from baseline in the CAPS-5 PTSD severity total score. The secondary endpoint was functional impairment per the Sheehan Disability Scale (SDS).

T: Primary outcome, and secondary endpoint measured at baseline and 18 weeks (~8 weeks after last therapy treatment session).

S: Phase 3, randomized (1:1), double-blind (participants + staff + verification of outcome by independent rater), multi-site (US, Canada, Israel), placebo-controlled trial

Primary conclusion(s): Significant improvement in CAPS-5 total severity score between baseline and the third therapy session (18 weeks later) for the MDMA arm versus placebo arm (mean change [SD]: MDMA, -24.4 [11.6] vs placebo, -13.9 [11.5]; between-group difference: 11.9, 95% CI 6.3 to 17.4, $P < 0.0001$; effect size, *Cohen’s d* = 0.91). SDS total scores were also significantly reduced from baseline to 2 months post-treatment for MDMA-treated participants compared to placebo-treated participants (mean change [SD]: MDMA, -3.1 [2.6] vs placebo, -2.0 [2.4]); P for between-group difference = 0.0116, $d = 0.43$). MDMA appeared safe, with either similar or fewer treatment-emergent events of suicidality, abuse, or QT interval prolongation compared to placebo.

Limitations (per authors): Enrolled smaller size than planned, though still met sample size for power calculation; minimal racial/ethnic diversity of participants; short follow-up; safety

reported by therapists, which could have compromised blinding; blinding was challenging, and may have been compromised for some participants.

2. Brewerton TD, Wang JB, Lafrance A, et al. MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. *J Psychiatr Res.* 2022;149:128-135.

P: Adults with severe PTSD without an active purging eating disorder (n = 89 participants; 82 completers); at baseline, 15% of participants had clinically elevated EAT (Eating Attitudes Test)-26 scores, and an additional 31.5% were classified as “at-risk”

I/C: Refer to Mitchell et al. 2021

O: Between-group change in baseline-adjusted EAT (Eating Attitudes Test)-26 self-reported questionnaire scores

T: Time to follow-up EAT-26 measurement *not reported*, measured at end of study (visit 20)

S: *Exploratory analysis* of a pre-specified measurement from the randomized, double-blind, placebo-controlled phase 3 trial (refer to Mitchell et al. 2021)

Primary conclusion(s): Among participants finishing the trial, a significantly larger decrease in EAT-26 score from baseline to follow-up was observed in the MDMA-treated arm versus PBO arm (mean change [SD]: MDMA, -3.04 [6.24] vs placebo, -0.68 [8.04]; P = 0.0335 for between group difference; effect size [*Hedges g*] = 0.33).

Limitations (per authors): Analysis was only performed on participants with full data, including only those completing the trial, which may introduce bias; small sample size for subgroup analysis; post-treatment BMI was not collected for the full study sample

3. Nicholas CR, Wang JB, Coker A, et al. The effects of MDMA-assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD. *Drug Alcohol Depend.* 2022;233:109356.

P: Adults with severe PTSD. Mild or moderate (in early remission) alcohol or cannabis use disorders were allowed, but other substance use disorders (SUD) within the prior 12 months were excluded (n = 89 participants; 82 completers); at baseline, ~25% of participants had a history of alcohol use disorder and 17% had a history of a SUD.

I/C: Refer to Mitchell et al. 2021

O: Change in alcohol use disorder identification test (AUDIT) and drug use disorder identification test (DUDIT) self-reported measures between baseline and study completion

T: Time to follow-up AUDIT/DUDIT measurement not reported, measured at end of study

S: *Exploratory analysis* from the randomized, double-blind, placebo-controlled phase 3 trial

Primary conclusion(s): Among finishers of the trial, a significantly larger decrease in AUDIT score from baseline to follow-up was observed in the MDMA-treated arm versus placebo arm (mean change [SD]: MDMA, -1.02 (3.52 versus placebo, 0.40 (2.70); $P= 0.0536$ for between group difference; effect size [*Hedges g*]= 0.45). No significant difference in change in DUDIT score between treatment arms was observed.

Limitations (per authors): Participants lacked severe alcohol use disorder, and any type of other substance use disorder (other than cannabis) at baseline.

Citations addressing the original phase 2 trial: Mithoefer et al. 2018 (NCT01211405)

4. Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 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. *Lancet Psychiatry*. 2018;5(6):486-497.

P: Adults with moderate-severe chronic PTSD (CAPS-IV score ≥ 50 ; mean baseline score of ~82 to 89) with trauma from serving in wars, or as a firefighter or police officer. Participants must have failed or not tolerated prior treatments, and psychotropic medication other than sedative/hypnotics or as-needed anxiolytics used outside of drug sessions (total n randomized = 26)

I: *During blinded trial period:* MDMA [(75 mg or 125 mg given as an initial dose plus optional supplemental dose 1.5 to 2 hours later) *two times*, during treatment sessions] plus therapy by a male and female therapist co-team (3, 90-min 'preparatory' sessions pre-treatment plus two 8-hour treatment sessions, separated by ~4 weeks plus two 'integration' sessions following each treatment session and separated by about 1 week). *During the unmasked crossover follow-up period:* MDMA 125 mg plus co-team led therapy (1 treatment session plus 3 'integration' sessions)

C: *During blinded trial period:* active control (low-dose MDMA, 30 mg) plus therapy, as per the MDMA intervention groups. *During the unmasked crossover follow-up period* (crossover of people receiving MDMA 30-75 mg in the blinded period): MDMA 100-125 mg plus co-team led therapy (1 'preparatory' sessions + 3 treatment session about 4 weeks apart + 3 'integration' sessions)

O: Mean change in CAPS-4 total score

T: Primary *blinded* outcome measured between baseline and ~4 weeks after the last therapy treatment session. *During the unmasked crossover period:* 2-month follow-up after 3rd MDMA treatment session, and a 12-month follow-up (12 months after last 100-125 mg MDMA dose)

S: Phase 2, randomized (1 MDMA 30 mg: 1 MDMA 75 mg: 2 MDMA 125 mg), double-blind (participants + investigators + outcome verification by independent rater), single-site (US outpatient clinic) trial. After the time of the primary outcome measurement, there was a crossover, unmasked follow-up period.

Primary conclusion(s): Significant reductions in mean CAPS-IV score between baseline and 4 weeks after the second MDMA treatment session were observed for both MDMA intervention groups compared to the low-dose (30 mg) (mean change [SD]: MDMA 125 mg, -58.3 [9.8] versus MDMA 75 mg, -44.3 [28.7] and MDMA 30 mg, -11.4 [12.7]; P=0.001 for comparison to 30 mg). During the crossover period, the group initially receiving 75 mg failed to show a significant decrease in PTSD symptoms after receiving 100-125 mg; however, the group initially receiving 30 mg demonstrated significant decreases after receipt of the higher MDMA dose. PTSD symptoms were significantly reduced at the 12-month follow-up relative to baseline for all study arms. Treatment-emergent adverse drug events (ADE) were reported by 20 patients (85 total events, 4 considered serious). One serious ADE ("an acute increase in premature ventricular contractions"⁶⁷ in a patient with a history of this condition) was considered possibly drug-related; the affected patient recovered and lacked evidence of lasting damage.

Limitations (per authors): Small sample size that included primarily white men; possibly compromised blinding; the 12-month follow-up is limited by the lack of a comparison group that did not receive higher-dose MDMA (125 mg).

5. Barone W, Beck J, Mitsunaga-Whitten M, Perl P. Perceived Benefits of MDMA-Assisted Psychotherapy beyond Symptom Reduction: Qualitative Follow-Up Study of a Clinical Trial for Individuals with Treatment-Resistant PTSD. *J Psychoactive Drugs*. 2019;51(2):199-208.

[NCT not reported, but described as follow-up to the Mithoefer et al. 2018 study](#)

P: Adults with moderate-severe treatment-resistant PTSD with trauma from serving in wars, or as a firefighter or police officer (total n randomized = 26; participants in follow-up sample = 19)

I/C: Refer to Mithoefer et al. 2018. At the time of follow-up all participants had received MDMA-assisted therapy.

O: Themes via interpretative phenomenological analysis of participant semi-structured interviews

T: Twelve month follow-up after trial completion

S: Retrospective qualitative follow-up study of a phase 2, randomized, double-blind trial

Primary conclusion(s): "All participants reported experiencing lasting personal benefits and enhanced quality of life that extend beyond quantifiable symptom reduction"⁶⁸

Limitations (per authors): Retrospectively-designed study (limited to available recorded interviews from the trial follow-up); information available for 19 of 26 trial participants; interviews were originally conducted by one of the study therapists with established patient rapport; generalizability to people other than white males.

Citations addressing the original phase 2 trial: Ot'alora et al. 2018 (NCT01793610)

6. Ot'alora GM, Grigsby J, Poulter B, et al. 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. *J Psychopharmacol.* 2018;32(12):1295-1307.

P: Adult with moderate-severe (CAPS-IV score ≥ 50) chronic PTSD that failed to response to at least 1 regimen of psychotherapy or drug treatment (total n randomized = 28)

I: *During blinded trial period:* MDMA [(100 or 125 mg initial dose + optional supplemental dose 1.5 hours later) two times, during treatment sessions] plus therapy (three 90-min 'preparatory' sessions pre-treatment plus two, 8-hour treatment sessions, separated by ~1 month plus 3 'integration' sessions following each treatment session 1 week apart, including daily phone contact after 1st integration session). *During the unmasked crossover follow-up period:* MDMA 100-125 mg plus co-team led therapy (1 treatment session + 3 'integration' sessions)

C: *During blinded trial period:* active control (low-dose MDMA, 40 mg) plus therapy matching the MDMA intervention groups. *During the unmasked crossover follow-up period* (crossover of people receiving MDMA 40 mg in the blinded period): MDMA 100-125 mg plus co-team led therapy (1 'preparatory' session + 2 treatment sessions about 1 month apart + 3 'integration' sessions; followed by 1 treatment session + 3 'integration' sessions after the endpoint measurement post 2 treatment sessions)

O: Mean change in CAPS-4 total score

T: Primary blinded outcome measured between baseline and ~1 month after the last therapy treatment session (2 treatment sessions). During the unmasked crossover period: 2-month follow-up after 3rd MDMA treatment session, and a 12-month follow-up (12 months after last 100-125 mg MDMA dose)

S: Phase 2, randomized(~2 MDMA 125 mg: 1.5 MDMA 100mg: 1 MDMA 40 mg), double-blind (participants + investigators + outcome verification by independent rater) dose-finding, single site (US outpatient clinic) trial. After the time of the primary outcome measurement, there was a crossover, unmasked trial follow-up period.

Primary conclusion(s): Numerically larger decreases in PTSD symptom severity from baseline to 1 month after 2 MDMA sessions were observed in the intention-to-treat analysis of the MDMA 125 mg arm (mean change [SD]: -26.3 [29.5]) and MDMA 100 mg arm (mean change [SD]: -24.4 [24.2]) compared to the MDMA 40 mg arm (mean change [SD]: -11.5 [21.2]); the

difference compared to the low-dose arm was statistically significant by per-protocol analysis. Significant improvements in PTSD symptoms relative to baseline were detected at 12 months. Authors report a lack of serious ADE attributable to MDMA.

Limitations (per authors): Small sample size that included primarily white women; possibly compromised blinding; at the 12 month follow-up, there was not a comparison group and participants were aware of initial group assignments.

Citations addressing the original phase 2 trial: Oehen et al. 2013 (NCT00353938)

7. Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of psychopharmacology*. 2013;27(1):40-52.

This study secondarily aimed to confirm findings from Mithoefer et al. 2011 in a new setting.

P: Adults (mean age = 41.4) with treatment-resistant PTSD (CAPS score ≥ 50 with a history of ≥ 6 months of psychotherapy as well as 3 months of treatment with an SSRI). Total n randomized = 14; total n included in analysis = 12 (2 additional patients were randomized but discontinued participation after the first MDMA treatment session).

I: Three full-dose MDMA administrations sessions, each consisting of 125 mg MDMA followed by another 62.5 mg MDMA dose administered 2.5 hours later during full-day psychotherapy sessions. In addition, 12 non-drug psychotherapy sessions were performed.

C: Three low-dose MDMA administration sessions, each consisting of 25 mg of MDMA followed up by another 12.5 mg MDMA dose administered 2.5 hours later during full-day psychotherapy sessions and an additional 12 non-drug psychotherapy sessions. Considered to be an “active placebo” at low doses that are not expected to produce significant applicable effects.

O: Change in mean CAPS score

T: CAPS scores measured at baseline, 3 weeks after MDMA session 2, 3 weeks after MDMA session 3, and 2 months, 6 months, and 12 months after MDMA sessions 3. Referred to as T0-T5, respectively.

S: Phase 2, double-blinded, randomized (2:1), “active placebo” controlled experimental trial in German-speaking Switzerland. The masked period was followed by an open-label cross-over period where “active placebo” participants received full-dose MDMA (3 MDMA sessions plus 12 non-MDMA therapy sessions), and high-dose MDMA non-responders optionally received

additional higher-dose MDMA (150 mg plus supplemental 75 mg during 2 sessions with 7 non-drug therapy sessions).

Primary Conclusions: Lack of statistically significant improvement in mean CAPS score from baseline to 3 weeks after MDMA session 3 (end of blinded period) for the full-dose versus active placebo comparison (mean CAPS score change from T0 to T2 [SD]: full-dose MDMA, -15.6 (18.1) versus low-dose active placebo, -3.2 CAPS [15.3]; P=0.066). Statistically significant improvement in secondary outcome of posttraumatic diagnostic scale (PDS) score for high-dose MDMA treated participants vs active-placebo treated patients from T0 to T2 occurred (P=0.014). Authors deny any serious MDMA-related ADE.

Limitations (per authors): Small sample size that was underpowered for safety outcomes and likely unreliable for efficacy outcomes; generalizability concerns based on population of primarily female Europeans; 2:1 ratio of intervention: control assignment; possibility of unmasking during the blinded period; some patients in the low-dose MDMA control group exhibited a higher than expected response to the supposedly inactive dose; therapy adherence was assessed in a post-hoc analysis (not reported) and some protocol deviations favoring increased directiveness of therapy occurred.

Summary studies from multiple phase 2 trials

8. Ponte L, Jerome L, Hamilton S, et al. Sleep Quality Improvements After MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder. *J Trauma Stress*. 2021;34(4):851-863.

[NCT01958593](#), [NCT01211405](#), [NCT01689740](#), [NCT01793610](#) (trial IDs: MP-8 [US], MP-12 [US], MP-4 [Canada], MP-9 [Israel])

P: Adults with moderate-severe PTSD (CAPS-4 score ≥ 50 or ≥ 60 in 1 trial) [total n randomized = 68; 62 with complete data]

I: *Varied by trial*; active-dose MDMA (75-125 mg)-assisted therapy (2 blinded; 1 open-label); see phase 2 trial descriptions for examples of the regimens

C: *Varied by trial*; control-dose MDMA (0-40 mg)-assisted therapy (2 blinded); see phase 2 trial descriptions for examples of the regimens

O: Change in sleep quality based on the Pittsburgh Sleep Quality Index (PSQI) self-reported questionnaire

T: Blinded measurements were made 1 month after the 2nd MDMA/placebo-assisted therapy session; additional open-label follow-up occurred: treatment-end, occurring 2 months after the 3rd therapy session for the active-MDMA arm and control-MDMA arm, and a 12-month follow-up, occurring 12 months after the final open-label MDMA therapy session.

S: *Exploratory* pooled secondary analysis of 4 phase 2, placebo-controlled, randomized trials. These trials included an initial blinded, parallel group period followed by an open-label cross-over period when participants that initially received control-dose MDMA switched to receive active MDMA treatment. During the open-label period, the active-MDMA group completed 1 additional MDMA-therapy session, and the control-MDMA arm completed 3 MDMA-assisted therapy sessions.

Primary conclusion(s): One to 2 months after 2 therapy sessions, during the blinded period, significantly improvement in sleep quality relative to baseline occurred in the active-MDMA arm (mean PSQI change [SD]: -3.53 [5.03]) relative to the control-MDMA arm (mean PSQI change [SD]: 0.56 [3.05]); $P = 0.003$ for between group difference; effect size (*Hedges g*) = 0.88). Compared to baseline, all participant's sleep quality significantly improved at treatment-end, and at 12 months of follow-up (these measurements did not have a control group as all participants had received active-MDMA). Improvements in PTSD severity scores were also reported.

Limitations (per authors): Small sample size; generalizability, given primarily white participants; subjective, self-reported outcome measurements

9. Gorman I, Belser AB, Jerome L, et al. Posttraumatic Growth After MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder. *J Trauma Stress.* 2020;33(2):161-170.

NCT not reported; includes data from studies MP-4 (not published), MP-8 (Mithoefer et al. 2018), and MP-12 (O'Alora et al. 2018)

P: Adults with moderate-severe PTSD based on CAPS-4 total scores of ≥ 50 (MP-8 or MP-12) or ≥ 60 (MP-4)

(Total $n = 45$ in the MDMA arm, and $n = 15$ in the placebo/low-dose MDMA arm)

I: MDMA 75-125 mg during the treatment therapy session x 2 plus co-team (male + female) 'manualized' therapy (three, 90-minute 'preparatory' sessions, two 8-hour treatment sessions ~1 month apart, which are each followed by three, 90-minute 'integration' sessions)

C: Placebo or low-dose 40 mg MDMA

O: Change in post-traumatic growth scores (measured by the 21-item PTG index, PTGI; total score ranges from 0 to 105) from baseline

T: Primary outcome was assessed 1 month after the 2nd MDMA/comparator treatment session. Additional follow-up was assessed after the cross-over period (participants crossover to MDMA 100-125 mg), and 12 months after the 3rd MDMA session (at that time all participants had been exposed to MDMA 100-125 mg three times plus therapy)

S: Pooled aggregate analysis of 3, phase 2 randomized triple-blind crossover trials (3 of 6 possible trials were selected since they measured posttraumatic growth)

Primary conclusion(s): At the end of the blinded period (after two, 75-125 mg MDMA doses plus therapy), MDMA-treated patients exhibited greater post-traumatic growth compared to patients receiving low-dose MDMA/placebo (Hedges g [a measure of standardized difference]: 1.14, 95%CI 0.49 to 1.78; $P < 0.001$). At the longest follow-up (12 months), a time point for which there is not a control group, 67.2% of patients no longer met criteria for having PTSD.

Limitations (per authors): Pooled data from 3 different trials with slight differences in study design; possible unmasking of participants and/or therapists; scores on the PTGI are self-reported and not validated with observed behaviors; participants primarily identified as white.

10. Jerome L, Feduccia AA, Wang JB, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology*. 2020;237(8):2485-2497.

[NCT00090064 \(MP-1\)](#), [NCT00353938 \(MP-2\)](#), [NCT01958593 \(MP-4\)](#), [NCT01211405 \(MP-8\)](#), [NCT01689740 \(MP-9\)](#), [NCT017993610 \(MP-12\)](#)

P: Adults with moderate-severe PTSD (CAPS-4 score ≥ 50 or ≥ 60 in 1 trial)

(Total n enrolled = 107; n = 91 completed long-term follow-up]

I/C: *Varied by trial.* All participants were eventually exposed to 2-3 MDMA-assisted therapy sessions. There was not an untreated control for the longitudinal analysis.

Initial higher-dose MDMA: *During blinded trial period:* MDMA [(75 mg, 100 mg, or 125 mg given as an initial dose + optional supplemental dose 1.5 to 2 hours later) two times, during treatment sessions] plus therapy by a male or female therapist co-team (three, 90-min 'preparatory' sessions pre-treatment plus two, 8-hour treatment sessions, separated by ~4 weeks plus three, 90-min 'integration' sessions); *during the unmasked crossover follow-up period:* MDMA active dose plus co-team led therapy (1 treatment session plus 3 'integration' sessions); two studies had only 2 MDMA therapy sessions (MP-1 and MP-9)

Initial placebo or low-dose MDMA: *During blinded trial period:* inert placebo or low-dose (25-40 mg) MDMA; *during the crossover period:* MDMA 100-125 mg, 2-3 psychotherapy sessions (as per the intervention arm); in 2 studies (MP-2 and MP-9) participants completed 3 blinded sessions.

O: Mean change from baseline in CAPS-4 total severity score

T: Assessed at trial completion (after 2-3 MDMA sessions during the blinded or open-label period); long-term follow-up about 12 months after last MDMA therapy session (or 3.8 years in 1 trial)

S: Within-group pooled analysis of 6 phase 2 RCTs that each included a parallel group double-blind period followed by a crossover and long-term follow-up periods; included sites in US, Canada, Switzerland, depending on the trial

Primary conclusion(s): Significantly improved in PTSD symptoms (CAPS-4 total severity score) between baseline and completion of the 2-3 MDMA therapy sessions (LS mean [SE]: -44.8 [2.82]; $P < 0.0001$), and between MDMA therapy completion and long-term follow-up (LS mean [SE]: -5.2.8 [2.29]; $P < 0.05$); the estimated effect size (Cohen's d) was 1.58 and 0.23 for the aforementioned follow-up periods, respectively. Most participants described benefiting from treatment (56% did not meet PTSD diagnostic criteria at study completion), and "...a minority reported harms from study participation."⁶⁹

Limitations (per authors): Lack of untreated control for the analysis (*investigators examined within participant changes from baseline and considered the MDMA-exposed data for intervention and control patients*); for the long-term follow-up, some participants continued other interventions including therapy after the study period so any benefits could also be attributable to other treatments; population and intervention heterogeneity, though the statistical model adjusted for some potential covariates.

11. Mithoefer MC, Feduccia AA, Jerome L, et al. 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. *Psychopharmacology*. 2019;236(9):2735-2745.

[NCT00090064](#), [NCT00353938](#), [NCT0195893](#), [NCT01211405](#), [NCT01689740](#), [NCT01793610](#)

This study informed design of the phase 3 trials, influencing selection of 3 MDMA-assisted therapy sessions instead of 2.

P: Adults with moderate-severe PTSD (CAPS-4 score ≥ 50 or ≥ 60 in 1 trial)

(Total n enrolled = 105, with 8 (7.6%) of participants not completing the study)

I: *Varied by trial. During blinded period:* MDMA [(75 mg, 100 mg, or 125 mg given as an initial dose plus optional supplemental dose 1.5 to 2 hours later) two times, during treatment sessions] plus therapy by a male or female therapist co-team (three 90-minute 'preparatory' sessions pre-treatment plus two, 8-hour treatment sessions, separated by ~4 weeks plus three 90-minute 'integration' sessions); *during the unmasked crossover period:* MDMA active dose plus co-team led therapy (1 treatment session plus 3 'integration' sessions); two studies completed only 2 MDMA therapy sessions (MP-1 and MP-9)

C: *Varied by trial. During blinded period:* inert placebo or low-dose (25-40 mg) MDMA; *during the unmasked crossover period:* MDMA 100-125 mg, 2-3 psychotherapy sessions (as per the intervention arm); in 2 studies (MP-2 and MP-9), participants completed 3 blinded sessions

O: Mean change from baseline in CAPS-4 total severity score

T: Assessed at trial completion, 1-2 months after 2-3 MDMA-assisted treatment sessions

S: Pooled analysis of 6 phase 2 RCTs with similar study designs that included a parallel group double-blind period followed by a crossover and long-term follow-up periods; included sites in US, Canada, Switzerland, depending on the trial

Primary conclusion(s): Significantly improved in PTSD symptoms (CAPS-4 total severity score) between baseline and completion of 2 MDMA therapy sessions for the experimental group versus control group (mean between group difference [SE]: -22.0 [5.17]; $P < 0.001$); the estimated effect size (Cohen's d) was 0.8. Investigators also describe improvements in the proportion of MDMA-treated participants versus control participants with symptoms meeting PTSD diagnostic criteria (statistical significance not reported), and in depression symptoms (not statistically significant). There is limited data limiting the ability to draw conclusions, but investigators report that there appears to be a greater proportion of treatment responders after 3 MDMA-assisted therapy sessions compared to 2 MDMA-assisted therapy sessions. Regarding safety, although considered well-tolerated overall, some AE were reported more frequently in the MDMA-treated versus control participants (eg, anxiety, dizziness, jaw clenching/pain, nausea, no appetite, depressed mood, irritability, and panic attack). Most ADE were reported during the MDMA treatment sessions or within the week following the session.

Limitations (per authors): The majority of participants and therapists identify as white; population and intervention heterogeneity across the RCTs; risk of unblinding; during the third MDMA session, participants may have received MDMA while blinded or as open-label

Citations addressing the original pilot trial: Mithoefer et al. 2011 (NCT00090064)

12. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of (+/-) 3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *Journal of psychopharmacology*. 2011;25(4):439-452.

P: Adults ages 21-70 years meeting DSM-IV-R criteria for crime or war-related, chronic moderate-severe PTSD (defined as a CAPS score ≥ 50), refractory to both 6+ months of psychotherapy and 3+ months of pharmacotherapy, following at least 3 months of psychotherapy after tapering and discontinuing all psychotropic medications except as-needed sedative-hypnotics or anxiolytics

(Total n randomized = 23)

I: MDMA 125 mg administered in two 8-10-hour experimental non-directive psychotherapy sessions 4 weeks apart (participants were also offered a supplemental MDMA 62.5 mg dose 2-2.25 hours after the initial dose). Each experimental session followed two 90-minute introductory sessions with therapists and was followed by an overnight stay. Each all-day session was followed by two 90-minute psychotherapy sessions the next morning and then weekly thereafter.

C: Inert placebo (lactose) administration with psychotherapy sessions that matched the active arm

O: Change in mean CAPS (versions not stated) score from baseline. Difference in percentages with clinical response from baseline.

T: Primary outcome measured at day 4 after each experimental session and 2 months after completion of the 2nd session

S: Randomized (60% MDMA: 40% placebo with replacement of any dropouts), double-blind, single-site (US), placebo-controlled trial

Primary conclusion(s): Significantly greater decrease in mean PTSD scale scores for MDMA versus placebo at all 3 time points. Rate of "clinical response" (defined as a $>30\%$ reduction in CAPS total score from baseline) was 10/12 (83%) with MDMA versus 2/8 (25%) with placebo. No serious drug-related adverse events, adverse neurocognitive effects, or blood pressure increases.

Limitations (per authors): Small sample size; homogenous sample of White female patients; baseline differences in prior psychotherapy that favored the treatment group; transparency of blinding for subjects

13. Mithoefer MC, Wagner MT, Mithoefer AT, et al. Durability of improvement in post-traumatic stress disorder symptoms and absence of harmful effects or drug dependency after 3,4-methylenedioxymethamphetamine-assisted psychotherapy: a prospective long-term follow-up study. *Journal of psychopharmacology*. 2013;27(1):28-39.

P: Adults with crime or war-related, treatment-refractory chronic, moderate to severe (ie, with baseline CAPS score of ≥ 50) PTSD, refer to Mithoefer et al. 2011.

(Total n randomized = 23; total n included in this descriptive extension study = 19)

I/C: There was not a comparator in this long-term, single-arm extension study of participants that received MDMA-assisted therapy during the blinded period followed

by 1 additional MDMA-assisted therapy session in the unmasked period (initial MDMA arm), and participants that received 2-3 MDMA-assisted therapy during the open-label crossover period (initial placebo arm). In both arms, each experimental (placebo or MDMA) session followed two 90-minute introductory sessions with therapists and was followed by an overnight stay. Each all-day session was followed by two 90-minute psychotherapy sessions the next morning and then weekly thereafter.

Initial MDMA arm: MDMA 125 mg with an optional 62.5 mg dose 2-2.5 hours later (amendment allowed for approximately half of participants) administered in two 8-10-hour experimental psychotherapy sessions 4 weeks apart followed by a third open-label 8-10-hour experimental psychotherapy session 2 months following the second; or Initial placebo arm: Inert placebo administered in two 8-10-hour experimental psychotherapy sessions 4 weeks apart, followed by open-label MDMA 125 mg with an optional 62.5 mg dose 2-2.5 hours later (amendment allowed for approximately half of participants) administered in two 8-10-hour experimental psychotherapy sessions 4 weeks apart. Approximately half of participants also received a third 8-10-hour experimental MDMA-assisted therapy session.

O: Change from end-of-treatment in Clinician-Administered PTSD Scale (CAPS) since completion of the final MDMA session

T: Time to primary outcome varied from 17.3 to 74.3 months after completion of the final MDMA-assisted therapy session

S: Descriptive long-term follow-up of treated participants from a randomized, double-blind, single-site (US), placebo-controlled trial that was followed by an unmasked, crossover period

Primary conclusion(s): Mean CAPS scores were not statistically significantly different from end-of-treatment to long-term follow-up. Two participants relapsed during follow-up.

Limitations (per authors): Only 16 of 19 subjects completed long-term follow-up assessments; there was no meaningful control group; 8 of 19 subjects were still in psychotherapy and 12 of 19 were taking psychiatric medicines; small sample size.

14. Corey VR, Pisano VD, Halpern JH. Effects of 3,4-Methylenedioxymethamphetamine on Patient Utterances in a Psychotherapeutic Setting. *J Nerv Ment Dis.* 2016;204(7):519-523.

[NCT not listed, but authors reported using data from the same trial as Mithoefer et al. 2011](#)

P: Adults with refractory moderate-severe PTSD (baseline CAPS score ≥ 40) resulting from crime or war, refer to Mithoefer et al. 2011 (total n randomized = 23; participants with usable data for this analysis = 20)

I/C: See Mithoefer et al. 2011

O: Frequencies of patient utterances from therapeutic sessions that were empathic (regarding others' emotions), entastic (requesting or appreciating physical touch), or ensuic (describing a change in their sense of themselves) by blinded scorers

T: Primary outcome measures were taken during the first experimental therapeutic sessions (visit 5); CAPS scores were measured 4 days after this session.

S: Randomized, double-blind, single-site (US), placebo-controlled trial

Primary conclusion(s): Compared to placebo, MDMA-treated patients produced higher numbers of scored utterances versus placebo ($P < 0.01$), including ensuic, empathic, and entactic utterances. A higher number of scored utterances correlated with lower posttreatment CAPS scores (Pearson's $r = -0.506$, $P = 0.023$).

Limitations (per authors): None mentioned

15. Wagner MT, Mithoefer MC, Mithoefer AT, et al. Therapeutic effect of increased openness: Investigating mechanism of action in MDMA-assisted psychotherapy. *J Psychopharmacol.* 2017;31(8):967-974.

This study aimed to investigate the relationship between personality changes (neuroticism and openness) and improvement in PTSD symptoms as a secondary analysis of data from Mithoefer et al. 2011 and Mithoefer et al. 2013. Reporting of the methods and results is unclear, so the following is our best interpretation.

P: Patients who participated in the MDMA-assisted study by Mithoefer et al. 2011 (ie, CAPS score ≥ 50 with refractory PTSD resulting from crime or war)

(Total n randomized = 23; participants with usable data for this analysis = 20; n = 16 providing long-term follow-up data)

I/C: Refer to Mithoefer et al. 2011. After the 2-month double-blinded period, placebo patients were allowed to receive 2 experimental MDMA-assisted therapy sessions (2 experimental MDMA sessions and 11 non-drug sessions) as per the MDMA arm during the original blinded period. A smaller proportion of patients were also assigned to a 3rd open-label MDMA-assisted therapy session (1 experimental session plus 3 non-drug sessions; n = 5 initially MDMA-assigned patients, and n = 4 initially placebo-assigned patients).

O: Change in Openness and Neuroticism Scales of the Revised NEO Personality Inventory (NEO PI-R) from baseline to 2 months and long-term follow-up. Global CAPS scores at 2 months and long-term follow-up while adjusting for change in Openness or Neuroticism from baseline to 2 months using repeated measure ANOVA.

T: Primary outcome measured at 2 months and long-term follow-up (mean 45.4 months)

S: Subgroup analysis using data from a randomized, double-blind, single-site (US), placebo-controlled trial, and a long-term, single-arm open-label follow-up of the trial

Primary conclusion(s): At 2-month follow-up, differences in CAPS scores were no longer significant for MDMA versus placebo when controlling for change in Openness

scores ($P=0.246$); by contrast, CAPS score decreases remained significantly better for MDMA versus placebo when controlling for Neuroticism scores ($P=0.02$). At long-term follow-up of participants that all received MDMA-assisted therapy (ie, including MDMA and initially placebo arms), there were significant changes in Neuroticism and Openness compared to baseline ($P<0.05$).

Limitations (per authors): Patients and therapists were able to correctly guess treatment assignments; main outcome measures are based on subjective report; sample size was small.

MDMA for Social Anxiety Disorder in Autistic Adults (NCT02008396)

16. Danforth AL, Grob CS, Struble C, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology*. 2018;235(11):3137-3148.

P: Autistic adults (age ≥ 21 years) with social anxiety disorder (Liebowitz Social Anxiety Scale [LSAS] score ≥ 60)

(Total n randomized = 12)

I: MDMA-assisted therapy, including MDMA at escalating doses per experimental session: 4 participants received MDMA 75 mg followed by 100 mg, and the other 4 received MDMA 100 mg followed by 125 mg. Therapy included 3 'preparatory' sessions (60-90 minutes each) plus 2 experimental MDMA sessions (about 8 hours each) separated by 1 month, which were followed by 3 'integrative' therapy sessions (60-90 minutes each) and were separated by 1 week. Preparatory and integrative therapy sessions followed a "standardized mindfulness-based therapy"⁷⁰ approach.

C: Matched inert placebo plus therapy as per the MDMA arm

O: Mean difference in LSAS score from baseline to follow-up; standardized placebo-corrected effect size calculated using Cohen's d

T: Primary outcome was 1 month after the 2nd MDMA session. Differences from baseline to 6 months were also calculated.

S: Phase 2, dose-finding, single-site (US), randomized (2 MDMA:1 placebo), placebo-controlled, double-blind trial. Blinding ended at 6 months; at this time, placebo patients were allowed to receive 2 MDMA-assisted therapy sessions.

Primary conclusion(s): Greater improvement in social anxiety symptoms from baseline to 1 month and 6 months after the last MDMA session for MDMA-treated participants compared to placebo-treated participants (mean change from baseline to 1 month [SD]: MDMA, -44.4 [14.8]; placebo, -19.3 [18.8]; $P=0.037$ for between-group difference; mean change from baseline to 6-months [SD]: MDMA, -47.7 [14.7]; placebo, -23.2 [18.0]; $P=0.036$ for between-group

difference). The treatment effect size (Cohen's d [95%CI]) at 1-month was 1.4 [-0.074 to 2.874], and 1.1 [-0.307 to 2.527] at 6 months.

Limitation(s): Small sample size; and participants were heterogeneous at baseline with regard to social anxiety severity and other psychiatric conditions.

MDMA for Anxiety Associated with Life-threatening Illness (NCT02427568)

17. Wolfson PE, Andries J, Feduccia AA, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: a randomized pilot study. *Scientific reports*. 2020;10(1):20442.

P: Adults (mean age of 55 years) with moderate-severe anxiety (baseline State Trait Anxiety Inventory [STAI]-Trait subscale score of ≥ 45) associated with life-threatening non-brain cancer, or non-dementing neurological illness that could safely taper off psychiatric medications. Confirmation of illness-associated anxiety was confirmed by structured interview to confirm DSM-IV criteria.

Many participants had a history of anxiety (83.3%), MDD (77.8%), PTSD (72.2%) and insomnia (61.1%). (Total n randomized = 18; 17 participants completed long-term follow-up)

I: Blinded period: MDMA 125 mg administered during two 8-hour experimental non-directive psychotherapy sessions separated by 2-4 weeks plus 9 non-drug 60-90 minute psychotherapy sessions. An optional second MDMA 62.5 mg dose 1.5 to 2.5 hours the initial dose was available. MDMA-assisted therapy sessions were preceded by 3 'preparatory' therapy sessions, and 'integrative' therapy sessions occurred the day after the experimental sessions and 2 additional times over the following month. Therapists also contacted participants for daily phone calls during the 7 days after an experimental session. **Crossover period:** participants received 1 additional MDMA-assisted therapy session and 3 integrative therapy sessions.

C: Blinded period: Matched inert placebo administered during two 8-hour experimental non-directive psychotherapy sessions with therapy sessions as per the MDMA arm. **Crossover period:** participants received a preparatory session followed by 2 MDMA-assisted therapy sessions with 3 integrative therapy sessions, and 1 additional MDMA-assisted therapy session/3 integrative session about 1 month later.

O: Mean change in STAI-trait subscale score. Change in STAI-state subscale score was a secondary outcome.

T: The primary outcome was change in STAI score from baseline to 1 month after the second blinded drug-assisted therapy session. STAI scores were also measured for long-term follow-up at 6 months and 12 months after the last MDMA-assisted therapy session for all participants (ie, initial MDMA arm and initial placebo arm).

S: Phase 2, randomized (3 MDMA: 1 placebo), single-site (US outpatient clinic), double-blinded, placebo-controlled clinical trial. After the double-blinded period, there was an unmasked crossover period followed by an uncontrolled, single-arm, long-term follow-up period.

Primary Conclusion(s): There was a non-statistically significant reduction in anxiety symptoms (STAI-Trait score) from baseline to 1 month after 2 drug-assisted therapy sessions for MDMA compared to placebo (mean change from baseline [SD]: MDMA, -23.5 [13.2] versus placebo, -8.8 [17.9]; $P = 0.0558$ for the between-group difference; between-group effect size [Hedges g] = 1.03, 95%CI -5.25 to 7.31). A similar non-statistically significant reduction for the secondary outcome of STAI-state scores for MDMA compared to placebo occurred (mean change from baseline to 1 month after last treatment [SD]: MDMA, -22.1 [17.9] versus placebo, -6.0 [15.8]; $P = 0.10$ for the between-group difference). At 6-month and 12-month follow-up, the mean STAI-Trait and mean STAI-state scores among all participants were statistically significantly lower than baseline ($P < 0.0001$ for both). Investigators considered MDMA to be well-tolerated by participants, with most treatment-emergent adverse events occurring more frequently with MDMA compared to placebo resolving within 1 week.

Limitations (per authors): Small sample size, lacking power to detect statistical significance; potential outlier in placebo group that responded unusually well to placebo psychotherapy; lack of diversity due to participants being primarily White females; long-term follow-up results lacked a control group and blinding that limits usefulness and interpretation of those results.

Other MDMA Citations

18. Curran HV, Wall M, Demetriou L, Carhart-Harris R, Fergusson B, Nutt D. S.23.02 - Effects of ecstasy on autobiographical memories: implications for MDMA assisted psychotherapy. *European Neuropsychopharmacology*. 2016;26:S145.

NCT not reported

Limited information is available since it is published as an abstract only. We could not verify that the study meets all eligibility criteria (eg, randomization, patient population with a mental health condition).

P: Not reported

I: MDMA-HCl 100 mg

C: Placebo

O: Recall and encoding of memories; measured by functional MRI (fMRI) and self-referent encoding (SRE) of descriptors in reference to oneself vs others (considered "neutral")

T: Not reported

S: Double-blinded trial with repeated measures using functional MRI imaging

Primary conclusion(s): Participants administered MDMA exhibited a significant reduction in medial prefrontal cortex/left insula activation during self-referential activities compared to people receiving placebo. There was enhanced hippocampal activity during favorable memories versus enhanced executive activity during negative memories among MDMA recipients; they rated favorable memories as more positive and negative memories as less negative compared to placebo recipients.

Limitations (per authors): Not reported

Psilocybin Studies

Psilocybin for Depression

Citations addressing the original phase 2b trial: Goodwin et al. 2022 (NCT03775200)

19. Goodwin GM, Stansfield SC, Hellersten DJ, et al. The safety and efficacy of COMP360 psilocybin therapy in treatment-resistant depression: results from a phase IIb randomized controlled trial. Poster presented at: 2022 American Psychiatric Association Meeting; May 2022; New Orleans, LA.

This is from a poster presented at a conference; fewer details are available, and it has not been peer-reviewed for publication in a journal.

P: Adults with moderate-severe (Hamilton Depression Rating Scale [HAM-D] score ≥ 18) treatment-resistant major depression. A 2-week antidepressant washout period preceded the trial.

(Total n randomized = 233)

I: Compass proprietary psilocybin (COMP360) 25 mg or 10 mg x 1 dose with one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

C: Low-dose (1 mg) Compass proprietary psilocybin (COMP360) x 1 dose with one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

O: The primary outcome was the least squares mean change from baseline in Montgomery-Åsberg Depression Rating Scale (MADRS) total score; a key secondary outcome was the persistence of a sustained response (maintenance of $\geq 50\%$ change in MADRS total score from baseline)

T: The primary outcome was measured 3 weeks after the psilocybin dose, and the key secondary outcome was assessed at week 12. The MADRS total score was assessed at baseline, day 2, week 1, week 3, week 6, week 9, and week 12.

S: International, multisite, randomized (1:1:1), double-blind, active-controlled, phase IIb trial

Primary conclusion(s): Psilocybin 25 mg, but not 10 mg, was superior to psilocybin 1 mg for improvement in depression symptoms (change in MADRS total score from baseline) 3 weeks after 1 dose (25 mg versus 1 mg, least squares mean difference in change in score [95%CI]: -6.6 [- 10.2 to -2.9]; $P < 0.001$). Numerically greater improvement in depression symptoms for 25 mg versus 1 mg were apparent on day 2 and 1 week after psilocybin treatment (no statistical analysis reported). The proportion of participants with a sustained response (assessed for week 12 versus week 3) were 16/79 (20.3%), 4/75 (5.3%), and 8/79 (10.1%), for the 25 mg, 10 mg, and 1 mg arms, respectively (no statistical analysis reported). Dose-related treatment-emergent ADE included headache, nausea, and dizziness. From day 2 to week 3, and after week 3 to week 12, there was a numerically (a statistical analysis was not reported) higher incidence of treatment-emergent serious adverse events (TESAE) in the psilocybin 25 mg and 10 mg arms, relative to the psilocybin 1 mg arm. The incidence of any TESAE from day 2 to week 3 was as follows: 5.1%, 5.3%, and 0% for 25 mg, 10 mg, and 1 mg, respectively. Events during this period included suicidal ideation, intentional self-injury, and hospitalization. The incidence of any TESAE from after week 3 to week 12 was as follows: 5.1%, 4.0%, and 1.3% for 25 mg, 10 mg, and 1 mg, respectively. Events during this period included suicidal behavior (reported for the 25 mg arm, but not the other arms), intentional self-injury (reported in the 10 mg and 1 mg arms), adjustment disorder, depression, drug withdrawal syndrome, and suicidal ideation. The investigators report that there was not any clinically significant changes in laboratory results or vital signs; a few patients in the psilocybin 25 mg arm experienced acute, transient changes in the cardiac QTcF interval.

Limitations (per authors): Not reported

20. Goodwin GM, Aaronson S, Dunlop BW et al. A multicenter, international, phase IIb randomized controlled trial of COMP360 psilocybin therapy in treatment-resistant depression: Changes in affect, anxiety, and further exploratory endpoints. Poster presented at: 2022 American Society of Clinical Psychopharmacology meeting; June 2022; Scottsdale, AZ.

This is from a poster presented at a conference; fewer details are available, and it has not been peer-reviewed for publication in a journal.

P: Adults with moderate-severe (HAM-D score ≥ 18) treatment-resistant major depression. A 2-week antidepressant washout period preceded the trial. (Total n randomized = 233)

I: Compass proprietary psilocybin (COMP360) 25 mg or 10 mg x 1 dose plus one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

C: Low-dose (1 mg) Compass proprietary psilocybin (COMP360) x 1_dose plus one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

O: Multiple exploratory outcomes; change from baseline on the following scales: positive and negative affect schedule (PANAS), generalized anxiety disorder scale - 7 items (GAD-7), work and social adjustment scale (WSAS), Sheehan disability scale (SDS), EQ-5D-3L and EQ visual analog scale (EQ-VAS), and digit symbol substitution test (DSST)

T: Outcomes assessed 3 weeks following the psilocybin dosing session

S: *Exploratory*, secondary analysis of an international, multisite, randomized (1:1:1), double-blind, active-controlled, phase IIb trial

Primary conclusion(s): Relative to baseline, at 3 weeks, the high-dose psilocybin arm (25 mg) exhibited significantly greater improvements in multiple exploratory outcomes compared to the low-dose comparator (1 mg). These outcomes (expressed as least squares mean difference in change from baseline [LSMD] for 25 mg versus 1 mg) included PANAS positive affect score (6.2, 95%CI 3.5 to 8.8), PANAS negative affect score (-3.2, 95%CI -5.6 to -0.8), GAD-7 score (-1.8, 95%CI -3.4 to -0.2), WSAS score (-5.1, 95%CI -8.4 to -1.8) and SDS score (-6.5, 95%CI -9.5 to -3.5). Statistical tests for differences for psilocybin 10 mg versus 1 mg were not reported, but the numerical changes from baseline for 10 mg were smaller than for 25 mg. No significant differences between treatment arms were observed for the quality of life (EQ-5D-3L) or cognition measure (DSST).

Limitations (per authors): Not reported

21. Goodwin GM, Aaronson S, Dunlop BW et al. A multicenter, international, phase IIb randomized clinical trial of COMP360 psilocybin therapy in treatment-resistant depression: Response and remission rates. Poster presented at: 2022 American Society of Clinical Psychopharmacology; June 2022; Scottsdale, AZ.

This is from a poster presented at a conference; fewer details are available, and it has not been peer-reviewed for publication in a journal.

P: Adults with moderate-severe (HAM-D score ≥ 18) treatment-resistant major depression. A 2-week antidepressant washout period preceded the trial. (Total n randomized = 233)

I: Compass proprietary psilocybin (COMP360) 25 mg or 10 mg x 1 dose plus one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

C: Low-dose (1 mg) Compass proprietary psilocybin (COMP360) x 1 dose plus one, 6-8 hour psychotherapy support session by a trained therapist during psilocybin administration

O: Treatment response ($\geq 50\%$ change), remission (MADRS total score ≤ 10), and sustained response (treatment response sustained to week 12) rates based on change from baseline in

the MADRS total score (key secondary endpoints); and change from baseline in QIDS-SR-16 (Quick Inventory of Depression Symptomatology-Self-Rated 16-item scale) total score (exploratory endpoint)

T: Response, remission, and QIDS-SR-16 scores were assessed at 3 weeks post-treatment. Sustained response was assessed at 12 weeks.

S: Analysis of 3 key secondary endpoints from an international, multisite, randomized (1:1:1), double-blind, active-controlled, phase IIb trial

Primary conclusion(s): Three weeks after treatment, the proportion of treatment responders relative to baseline was as follows: 25 mg (36.7%, 29/79) versus 1 mg (17.7%, 14/79). And the proportion of treatment remitters relative to baseline was as follows: 25 mg (29.1%, 23/79) vs 1 mg (7.6%, 6/79). Sustained responders, the percent meeting response criteria on the MADRS scale at 3 weeks, 12 weeks, and 6 or 9 weeks, were as follows: 25 mg (24.1%, 19/79) versus 1 mg (10.1%, 8/79). The percent of responders, remitters, and sustained responders was similar between psilocybin 10 mg and 1 mg arms. Investigators report the results for the percent responders and remitters descriptively, without a statistical analysis. At week 3 relative to baseline, change in depression symptoms in the past week (QIDS-SR-16) was significantly greater in the 25 mg arm than the 1 mg arm (least squares mean difference: -2.8 [95%CI -4.6 to -0.9]).

Limitations (per authors): Not reported

22. Goodwin GM, Marwood L, Mistry S et al. COMP360 psilocybin therapy in treatment-resistant depression: Results of a large randomized controlled phase IIb monotherapy study and an exploratory adjunctive therapy study. Poster presented at: 2022 American Society of Clinical Psychopharmacology; June 2022; Scottsdale, AZ.

This is from a poster presented at a conference; fewer details are available, and it has not been peer-reviewed for publication in a journal. This poster included results from 2 clinical trials: one is the phase 2b randomized, blinded, controlled trial ([NCT03775200](#)) and the other was a phase 2, open-label single arm trial of a small group of patients with treatment-resistant depression that received psilocybin 25 mg in addition to a serotonergic antidepressant ([NCT04739865](#)) that does not meet our criteria for the annotated bibliography.

P/I/C/O/T/S: See Goodwin GM et al.

Additional safety conclusion(s): The incidence of treatment-emergent adverse effects (TEAEs) per study arm during the entire double-blinded, controlled trial period (anytime through 12 weeks) was as follows: 25 mg (83.5%), 10 mg (74.7%), and 1 mg (72.2%). On day 1 (psilocybin dosing day), the most frequent TEAEs occurring numerically more with psilocybin 25 mg than psilocybin 1 mg were headache and nausea. Although a serious

suicidal ideation/behavior occurred (including 3 cases >4 weeks after psilocybin 25 mg, among patients lacking improvement in depression symptoms), investigators reported that mean change from baseline for the MADRS suicidal ideation item did not worsen for any treatment arm, and the change from baseline to worst reported Columbia-Suicide Severity Rating Scale Score was not worse in the 25 mg or 10 mg arm relative to 1 mg arm (details for these measurements were not reported).

Limitations (per authors): Not reported

Citations addressing the original phase 2 clinical trial: Carhart-Harris et al. 2021 (NCT03429075)

23. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of Psilocybin versus Escitalopram for Depression. *The New England journal of medicine*. 2021;384(15):1402-1411.

P: Adults (18 to 80 years old) with moderate to severe major depression (HAM-D 17 score ≥ 17 at baseline) without prior use of escitalopram. Other psychiatric treatments were discontinued ≥ 2 weeks, and psychotherapy was discontinued ≥ 3 weeks prior to starting the study drugs.

(Total n randomized = 59)

I: Psilocybin 25 mg x 2 doses separated by 3 weeks given with daily matched placebo; patients also received psychological support consisting of at least 6 visits over 6 weeks with a two-person therapist team. These visits included a preparatory visit 1 day before the drug-assisted session, a well-being focused support session during drug administration session 1, psychological debriefing 1 day after the drug session; and 3 weeks later, a similar drug administration session, followed by an integrative therapy session (“...involving open, attentive listening”) the next day, and a final psychological debriefing session 3 weeks later.

C: Escitalopram 10 mg daily titrated to 20 mg after 3 weeks given with psilocybin 1 mg x 2 doses separated by 3 weeks, given when the psilocybin 25 mg arm received their psilocybin dose; patients also received psychological support as per the psilocybin 25 mg arm.

O: Change in Quick Inventory of Depressive Symptomatology-Self-Report 16 items (QIDS-SR-16) score from baseline

T: The primary outcome was assessed at 6 weeks

S: Phase 2, parallel-group, randomized (1:1), double-blind, active-controlled trial

Primary result(s): At 6 weeks, change in depression symptom scores were similar between psilocybin- and escitalopram-treated participants (between group difference in change in scores from baseline: 2.0 points; 95%CI -5.0 to 0.9; $P = 0.17$). Secondary outcomes, such as response (ie, severity score reduced by >50%), tended to favor psilocybin. The incidence of adverse events was also similar in both treatment arms.

Limitations (per authors): No adjustment for multiple comparisons; short duration of use of escitalopram relative to its time to onset of effect; no assessment of blinding adequacy; and generalizability concerns due to a high proportion of patients being self-recruited (perhaps high interest in psilocybin), limited diversity of ethnic and socioeconomic backgrounds, and the severity of depression at baseline (most patients classified as moderate).

24. Daws RE, Timmermann C, Giribaldi B, et al. Increased global integration in the brain after psilocybin therapy for depression. *Nature medicine*. 2022;28(4):844-851.

This study reported results from a single-arm psilocybin trial, and from a blinded RCT (ie, [NCT03429075](#)). We focus on results contrasting the psilocybin and escitalopram arms from the blinded RCT. It is unclear, but it appears that this analysis was limited to within-group changes from baseline.

P: Adults with unipolar moderate-severe MDD; in the open-label single-arm trial, participants had treatment-resistant depression

(Total $n = 21$ patients receiving escitalopram, and 22 receiving psilocybin because some participants were excluded due to excessive head motion that interfered with measurements; the open-label trial included 16 participants)

I/C: Refer to Carhart-Harris et al. 2021. Open-label trial participants also received 2 doses of psilocybin (first 10 mg, then 25 mg) separated by 1 week.

O: Functional connectivity with a Pearson correlation coefficient calculated for mean signal fluctuations, transformed to Z scores. Brain network modularity, functional cartography, and dynamic flexibility were also calculated from functional magnetic resonance imaging (fMRI) data.

T: fMRI at baseline and 3 weeks and 1 day after psilocybin dose 2 (about 6 weeks from baseline); fMRI measurements for the open-label cohort were 1 day after the second dose of psilocybin

S: Eyes-closed fMRI data was collected from 2 clinical trials: (1) an open-label single-arm trial; and (2) a phase 2, randomized, blinded, active-controlled trial

Primary conclusion(s): There were decreases in brain network modularity (ie, increased flexibility) 3 weeks after the last dose of psilocybin relative to baseline among psilocybin-treated participants in the blinded trial (mean difference [95%CI]: -0.39 [-0.75 to -0.02]; $P = 0.039$; $d = 0.47$). In contrast, a significant difference between baseline and 3 weeks after treatment was not observed among escitalopram-treated participants (mean difference [95%CI]: -0.01 [-0.35 to 0.33]; $P = 0.95$; $d = 0.02$). In the psilocybin arm, improvement in depression severity correlated with the reduced network modularity; this correlation was not observed for escitalopram-treated patients. Similar results for psilocybin-correlated changes were observed in both trials.

Limitations (per authors): It is possible that psilocybin-mediated effects occur via a mechanism other than those calculated in this study; possibility of confounding due to fMRI collection methods (eg, possibility of head motion, or sleeping in the MRI), although authors designed the protocol to minimize these effects; failure to replicate “finer-grained cartography analyses”⁷¹; difficulties collecting sufficiently powered fMRI data, although others felt they were powered to estimate correlations.

Citations addressing the original clinical trial: Davis et al. 2021 (NCT03181529)

25. Davis AK, Barrett FS, May DG, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA psychiatry*. 2021;78(5):481-489.

P: Adults 21-75 years old with untreated moderate to severe MDD (GRID-HAMD score ≥ 17).

(Total n randomized = 27)

I: Immediate treatment: 2 escalating oral psilocybin doses (20 mg/70 kg and 30 mg/70 kg) administered a mean of 1.6 weeks apart in two, 11-hour supportive psychotherapy sessions; interventions were administered after two 8-hour preparatory sessions; ‘supportive psychotherapy’ included the availability of 2 facilitators with varying education levels (eg, bachelor’s, master’s, doctorate, and medical degrees) and professional disciplines (eg, social work, psychology, and psychiatry) to respond to participants’ physical and emotional needs during the 11-hour sessions.

C: Delayed treatment: no intervention other than weekly brief in-person or phone calls for assessment of symptoms was administered to wait-listed patients (controls) until after 8-week trial period

O: Standardized mean difference (SMD) of change from baseline in GRID-HAMD scores (calculated using Cohen’s d)

T: Primary outcome measured 1 and 4 weeks after completion of 2nd psilocybin treatment (corresponding to week 5 and week 8 from baseline)

S: Randomized (1:1 urn randomization[1] balancing age, sex, depression severity, and treatment resistance), open label, single-site (US), controlled (wait listed patients) trial

Primary conclusion(s): Significantly greater improvement in GRID-HAMD scores associated with psilocybin treatment ($P < 0.001$ for between-group difference in means at week 5 and week 8). Mean (SD) GRID-HAMD scores in the treatment group were 22.9 (3.6) at baseline and 8.0 (7.1) and 8.5 (5.7) at 1 and 4 weeks after treatment, respectively, versus 22.5 (4.4), 23.8 (5.4), and 23.5 (6.0) in the delayed-treatment group (ie, untreated wait-list comparators). Limited mild and transient adverse effects were observed during treatment sessions including blood pressure elevation (1 participant) and headache (33%).

Limitations (per authors): Antidepressants may have been prescribed by non-study clinicians; lack of blinding and 11% attrition[2]; short follow-up; small sample predominantly composed of White non-Hispanic participants; participants had low suicide risk and moderately severe depression; lack of placebo control; varying professional disciplines of facilitators, often lacking formal clinical training

26. Gukasyan N, Davis AK, Barrett FS, et al. Efficacy and safety of psilocybin-assisted treatment for major depressive disorder: Prospective 12-month follow-up. *Journal of psychopharmacology*. 2022;36(2):151-158.

P: Adults 21-75 years old with untreated moderate to severe MDD (GRID-HAMD score ≥ 17) (Total n randomized = 27; 24 participants included at follow-up)

I/C: Refer to Davis et al. 2021. At the time of long-term follow-up, all participants had received 2 oral psilocybin doses with 'supportive psychotherapy,' so there was not a long-term comparator arm.

O: Standardized mean difference (SMD) of change from baseline GRID-HAMD scores (calculated using Cohen's d)

T: Primary outcome was measured 3, 6, and 12 months after the 2nd psilocybin treatment

S: Single-arm, open-label (with blinded outcome evaluator) follow-up of a randomized, controlled trial

Primary conclusion(s): Findings support the *potential* durability of improvement in GRID-HAMD scores from baseline to 3-, 6-, and 12-months (Cohen $d = 2.0, 2.6, 2.4$, respectively). No drug-related serious adverse events occurred.

Limitations (per authors): About one-third of participants endorsed use of confounding medications (antidepressants) during the period between study completion and follow-up; lack of untreated comparator during the follow-up period; effectiveness could also be due to "expectancy effects", and this placebo-effect could be long-lasting; generalizability to patients underrepresented in the study population (eg, ethnicity other than White non-Hispanic) including higher-risk patients based on suicidality; small sample size.

27. Barrett F. In patients with major depressive disorder, psilocybin administration is associated with reduced amygdala response to negative affective stimuli and normalization of cortical glutamate one week after psilocybin, and improved cognitive flexibility one and four weeks after psilocybin. *Neuropsychopharmacology*. 2019;44:76-77.

NCT not reported, but based on the methods and authors, we believe these results to be from the same trial reported by Davis et al. 2021. Published as an abstract only, limiting

available information about the study. It is unclear whether investigators calculated within-group changes for all participants, or if the results contrast the immediate and delayed treatment groups prior to the delayed group receiving psilocybin.

P: Adults (mean age=40.3 years) diagnosed with MDD (total $n=21$; immediate treatment ($n=12$), or delayed ($n=9$) psilocybin treatment).

I: Immediate treatment with psilocybin in two administration sessions of different dosing (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg).

C: Delayed treatment with psilocybin in two administration sessions of different dosing (session 1: 20 mg/70 kg; session 2: 30 mg/70 kg).

O: The primary outcome is unclear. Authors report measuring cognitive flexibility using the Penn Conditional Exclusion Task (PCET) and verbal reasoning using the Penn Verbal Learning Test ($n = 18$ participants with measurements). In addition, for a subset of participants, proton magnetic resonance spectroscopy (MRS) of the anterior cingulate ($n=10$), right hippocampus ($n=10$), left hippocampus ($n=7$), and amygdala reactivity ($n=12$) was performed. Amygdala measurements occurred during a reactivity task to emotional facial expressions.

T: Measurements were collected at baseline (3 weeks before psilocybin session 1), and after psilocybin session 2 (1 week and 4 weeks later) for the PCET and verbal learning test. MRS was completed at baseline and 1 week after psilocybin session 2.

S: Randomized (via Urn randomization), waitlist-controlled trial. Outcomes were measured in a subset of trial participants that varied by the measurement.

Primary conclusion(s): Compared to baseline, measurements of glutamate were higher in the right hippocampus ($d = 0.59$; P not reported), and lower in the anterior cingulate cortex ($d = 0.53$; P not reported) at 1 week after the 2nd psilocybin administration. In the amygdala, the response to negative affective stimuli was lower 1 week after psilocybin dosing session 2 compared to baseline ($d = 0.61$; $P=0.026$). The changes in amygdala BOLD intensity signals in response to negative stimuli correlated with a reduction in depression severity (per GRID-HAMD) measured at 1 week after psilocybin dosing session 2 ($r=0.417$). Cognitive flexibility improved from baseline to 1 week ($P=0.045$) and 4 weeks ($P = 0.016$) after the 2nd psilocybin treatment. No changes in verbal reasoning were observed.

Limitations (per authors): Not reported.

Psilocybin for Psychological Distress, Depression, or Anxiety Associated with Life-threatening Cancer

Citations addressing the original clinical trial: Griffiths et al. 2016 (NCT00465595)

28. Griffiths RR, Johnson MW, Carducci MA, et al. Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial. *Journal of psychopharmacology*. 2016;30(12):1181-1197.

P: People (mean age = 56.3 years) with life-threatening cancer and depression or anxiety diagnoses meeting DSM-IV criteria

(Total *n* randomized = 56)

I: High-dose psilocybin first: oral psilocybin (22 or 30 mg/70 kg) administered in the context of monitored, 'nondirective' and 'supportive' therapeutic sessions of unspecified duration. Interventions were administered after two to three 8-hour preparatory sessions; monitors had varying education levels and professional qualifications.

C: Active-placebo psilocybin first: oral low (placebo-like) dose of psilocybin (1-3 mg/70 kg), masked to resemble the intervention, administered in therapeutic sessions matching the intervention arm

O: Change, SMD of change (Cohen's *d*), and percentage with clinically-significant change (ie, ≥50% decrease) in GRID-HAMD scores (depression) and HAM-A (anxiety) versus baseline

T: Primary outcome measured 5 weeks after the psilocybin treatment session

S: Randomized (1:1), masked inactive controlled, double-blind (participants and monitors), crossover, single-site (US) trial. In this crossover trial, participants were randomized as to whether they received the intervention in the first session, or the 2nd session 5 weeks later.

Primary conclusion(s): Significant improvement from baseline in GRID-HAMD and HAM-A scores in both groups 5 weeks after the first sequence ($P < 0.05$). SMDs of GRID-HAMD and HAM-A were significantly larger for high-dose versus control ($P < 0.001$). Percentages with clinical response were 92% for high-dose treatment versus 32% for control ($P < 0.01$). Mean GRID-HAMD scores (standard error of the mean [SEM]) for high-dose treatment were 22.9 (1.0) at baseline and 6.6 (1.0) at 5 weeks versus 22.3 (0.9) and 14.8 (4.5) for control. Mean HAM-A scores (SEM) for high-dose treatment were 25.7 (1.1) at baseline and 8.5 (1.2) 5 weeks after treatment versus 25.7 (0.9) and 16.6 (1.5) for control. Mild and transient adverse effects observed during treatment sessions including blood pressure elevations, nausea/vomiting, and psychological distress; no hypothesis testing was conducted on adverse effects.

Limitations (per authors): Session monitors varied in training and clinical backgrounds and 8.6% attrition at week 5 outcome assessment[3]; no statistical comparisons were made for adverse event risks; low-dose control may have been high enough to have some therapeutic activity; study not designed to assess efficacy beyond 5 weeks; study sample was small and homogenous.

Citations addressing the original clinical trial: Ross et al. 2016 (NCT00957359)

29. Ross S, Bossis A, Guss J, et al. Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial. *Journal of psychopharmacology*. 2016;30(12):1165-1180.

P: Adults (mean age 56.3) with cancer (62% with stages III or IV) and an anxiety-related diagnosis of either adjustment disorder with or without depressed mood or generalized anxiety disorder (per Structured Clinical Interview for DSM Disorders [Diagnostic and Statistical Manual of Mental Disorders-IV]). Most (59%) of participants reported previous treatment with an antidepressant or anxiolytic agent, but no participants were on any psychotropic agents at the time of enrollment.

(Total *n* randomized = 29).

I: Psilocybin-first: single dosing session of oral psilocybin (0.3 mg/kg) plus psychotherapy, followed by a single dose of oral niacin 250 mg 7 weeks later. Therapy consisted of 3 preparatory sessions (6 hours total) occurring 2-4 weeks before the psilocybin dose; 3 integrative session (6 hours total) occurring over 7 weeks following the psilocybin dose; and 3 additional integrative sessions (6 hours total) occurring within 6 weeks after the niacin dose. Psychotherapy sessions and post-medication integration sessions were conducted by a dyadic psychotherapy team.

C: Niacin first: single dosing session of oral niacin 250 mg plus psychotherapy followed by a single dose of oral psilocybin (0.3 mg/kg) 7 weeks later. Therapy was the same as the psilocybin-first arm-.

O: Pre-crossover mean score on various anxiety or depression scales, including: (1) Hospital Anxiety and Depression Scale [HADS] total score; (2) patient-reported anxiety (HADS-A); (3) depression (HADS-D); (4) Beck Depression Inventory (BDI); and Spielberger State-Trait Anxiety Inventory (STAI), including (5) patient-reported levels of the anxiety state (STAI-S) and (6) trait (STAI-T).

T: The primary outcome variables were measured prior to the crossover at 1 day and 6 weeks after the first dosing session, and 1 day before the second dosing session. Additional measurements after crossover (ie, when all participants had received psilocybin) were collected 1 day, 6 weeks and 26 weeks after the second dosing session.

S: Randomized, double-blind, controlled, crossover, single-site (US) trial. Patients were randomized to the sequence of interventions to receive either psilocybin or niacin first. The second dosing session (administration of the alternative therapy from the first) occurred 7 weeks after the first session.

Primary conclusion(s): Prior to crossover, mean scores for each of the primary outcome measures of anxiety and/or depression were significantly lower at each time point (1 day to 7 weeks after the first dosing session) for the psilocybin-first arm compared to the niacin-first arm (P varied from $P < 0.05$ to $P \leq 0.001$, depending on the scale and time point). The between-group effect size (Cohen's d) for the primary outcome measures at the pre-crossover time points (ie, the range of multiple reported measurements between 1 day and 7 weeks post-treatment) ranged from 1.36 to 1.39 for HADS total score, from 0.80 to 1.18 for HADS-A, from 0.98 to 1.32 for HADS-D, from 0.82 to 1.10 for BDI, from 1.18 to 1.45 for STAI-State, and from 0.95 to 1.40 for STAI-Trait scores. Psilocybin was associated with sustained anxiolytic and anti-depressant benefits (based on 60–80% of participants with a continued clinically significant response) in the total cohort (ie, after psilocybin use by all participants) at follow-up after 6.5 months.

Limitations (per authors): Small study size; minimal racial/ethnic diversity of participants that is reflective of the cancer patient population; the interpretation of the results at the end of the study was limited by the crossover design; the control (niacin) had “limited blinding”.

30. Agin-Liebes GI, Malone T, Yalch MM, et al. Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer. *Journal of psychopharmacology*. 2020;34(2):155-166.

P: Remaining individuals with life-threatening cancer and psychiatric distress that were alive and completed the original trial reported by Ross et al. 2016. Compared to the original trial population, this subpopulation had a higher proportion of gynecological cancers (33%), and none had a diagnosis of digestive cancers (versus 21% in the full trial population). At the second long-term follow-up (LTFU), 71% of participants were in partial or complete remission from their cancer.

(Total n randomized = 29; and 16 were alive at follow-up, with $n=15$ agreeing to participate in this study).

I/C: All participants received 1 dose of oral psilocybin 0.3 mg/kg and therapy. See Ross et al. 2016.

O: Mean score on various anxiety or depression scales, including: (1) Hospital Anxiety and Depression Scale [HADS] total score; (2) patient-reported anxiety (HADS-A); (3) depression (HADS-D); (4) Beck Depression Inventory (BDI); and Spielberger State-Trait Anxiety Inventory (STAI), including (5) patient-reported levels of the anxiety state (STAI-S) and (6) trait (STAI-T).

T: The average first LTFU occurred at 3.2 years (range 2.3–4.5 years) and the average second LTFU was at 4.5 years (range 3.5–5.5 years) after the original psilocybin dosing date.

S: Long-term, uncontrolled, within-subject follow-up of a RCT (refer to Ross et al. 2016)

Primary conclusion(s): One dose of psilocybin was associated with statistically significant within-person reductions from baseline in anxiety and/or depressive symptoms for each of the 6 primary outcome measures at the first and second long-term follow-up. With respect to all 6 outcome measures the *mean* within-person effect size (Cohen's *d*) for the change from baseline to follow-up was 1.90 (range 1.27 to 2.67) at 6.5 months, 1.30 (range 0.93 to 1.97) at the first LTFU, and 1.41 (range 0.86 to 1.89) at the second LTFU.

Limitations (per authors): Due to the crossover design of the original RCT, there is not a control group for the long-term follow-up period, so any changes cannot be directly attributed to psilocybin; improvements in participant's cancer symptoms could have also improved their psychological status; small study size; minimal racial/ethnic diversity of participants limiting generalizability.

31. Ross S, Agin-Liebes G, Lo S, et al. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. *ACS pharmacology & translational science*. 2021;4(2):553-562.

[NCT not reported, but it references including data from Ross et al. 2016 and Agin-Liebes et al. 2020.](#)

This secondary analysis included a subset of the original trial population, and thus may not have maintained the full benefits of balanced randomization.

P: Adults (mean age of 60.3) with cancer (72.8% with stages III or IV) and an anxiety-related diagnosis of either adjustment disorder, depressed mood or generalized anxiety disorder *with baseline suicidal ideation (score >0)*.

(Total *n* randomized = 29; *n* = 11 included in this analysis, 6 from the psilocybin-first arm and 5 from the niacin-first arm).

I: Psilocybin-first: single dose of oral psilocybin (0.3 mg/kg) plus psychotherapy, followed by a single dose of oral niacin 250 mg plus psychotherapy 7 weeks later. Refer to Ross S et al. 2016.

C: Niacin-first: single dose of oral niacin 250 mg (active comparator) plus psychotherapy, followed by a single dose of psilocybin 0.3 mg/kg 7 weeks later. Refer to Ross et al. 2016.

O: Suicidal ideation composite score from baseline using a post-hoc generated score combining two items on the Beck Depression Inventory-II and the Brief Symptom Inventory

questionnaires, and loss of meaning (LOM) score generated from 5 questions on the Demoralization Scale (DS) from baseline.

T: Suicidal ideation was measured at pre-crossover at 8 hours, 2 weeks, and 7 weeks after the first dosing session, and 6.5 months after the second dosing session. A composite suicidal ideation score was not created at the follow-up time points of 3.2 and 4.5 years. LOM was assessed pre-crossover at 2 weeks after the first dosing session, and post-crossover at 6.5 months, 3.2 years, and 4.5 years.

S: A post-hoc subgroup analysis of a randomized, double-blind, controlled, crossover study (Ross et al. 2016); and descriptive long-term follow-up study (pooling data from Agin-Liebes et al. 2020)

Primary conclusion(s): Among participants with a suicidal ideation score greater than 0 at baseline, the psilocybin arm showed statistically significant *within-group* reductions in suicidal ideation (SI) score from baseline at 8 hours, 2 weeks, and 7 weeks after the first dosing session ($P<0.05$); however, there was not a statistically significant difference in SI score between the psilocybin-first and niacin-first arms from 8 hours to 7 weeks after the dosing session. The psilocybin-first LOM scores were statistically significantly lower than the niacin-first arm scores 2 weeks after the first dosing session ($P=0.021$). A statistically significant within-group (all participants after receiving psilocybin) benefit at 6.5 months relative to baseline was also observed for SI and LOM ($P<0.001$ for both outcomes). Significant reductions in LOM score at 3.2 and 4.5 years of follow-up relative to baseline were also observed for the entire cohort ($P<0.001$).

Limitations (per authors): The original trial was not designed to evaluate the effects of psilocybin on suicidal ideation in patients with cancer; the evaluation of long-term benefits is limited by the crossover design of the original trial due to a lack of a proper control group; minimal racial/ethnic diversity of participants limiting generalizability; an established measure for suicidal ideation would have improved interpretability rather than using a post-hoc generated composite score.

32. Benville J, Agin-Liebes G, Roberts DE, et al. Effects of Psilocybin on Suicidal Ideation in Patients With Life-Threatening Cancer. *Biological Psychiatry*. 2021;89(9):S235-S236.

[NCT not reported](#), but it is described as a secondary analysis of a randomized, cross-over trial that appears to be the same trial reported by Ross et al. 2016.

Published as an abstract only. This abstract appears to be highly similar to the study by Ross et al. 2021 (citation #31). One difference is this abstract reports the outcome of desire for hastened death (DHD).

Ross et al. 2021 considered DHD is be highly correlated with loss of meaning, the outcome reported by Ross et al. 2021.⁷²

P: People with cancer and suicidal ideation at baseline

(Total *n* randomized = 29; *n* = 11 included in this analysis, 6 from the psilocybin-first arm and 5 from the niacin-first arm).

I: Psilocybin-first: single dose of oral psilocybin (0.3 mg/kg) plus psychotherapy with crossover to a single dose of oral niacin 250 mg plus psychotherapy 7 weeks later. Refer to Ross S et al. 2016.

C: Niacin-first: single dose of oral niacin 250 mg (active comparator) plus psychotherapy with crossover to a single dose of psilocybin 0.3 mg/kg 7 weeks later. Refer to Ross et al. 2016.

O: Changes in desire for hastened death (DHD), a score generated from two items on the Demoralization Scale.

T: Assessed at three pre-crossover timepoints, and several post-crossover timepoints, including at the 6.5 month timepoint, but exact outcome measurement times other than 6.5 months are not reported.

S: Secondary analysis of a randomized, double-blind, controlled, crossover study. Analysis performed per randomized group (ie, psilocybin vs niacin), but it was restricted to a subgroup of patients reporting suicidal ideation at baseline.

Primary conclusion(s): A statistically significant reduction in DHD was observed after psilocybin treatment (prior to crossover; $P < 0.01$). For three post-crossover timepoints, the entire cohort of psilocybin-treated participants demonstrated significant decreases in DHD relative to baseline ($P < 0.005$).

Limitations (per authors): Not reported

Citations addressing the original pilot trial: Grob et al. 2011 (NCT00302744)

33. Grob CS, Danforth AL, Chopra GS, et al. Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Archives of general psychiatry*. 2011;68(1):71-78.

P: Adults (ages 36 to 58 years) with advanced-stage non-brain cancer and reactive anxiety (ie, acute distress disorder, anxiety disorder due to cancer, adjustment disorder with anxiety). (Total *n* randomized = 12)

I: One moderate oral psilocybin dose (0.2 mg/kg) was administered in one of two 6-hour sessions spaced several weeks apart, which started the morning after entering the hospital treatment facility. During the other session, participants received niacin. Participants were

allowed to discuss subjective aesthetic, cognitive, affective, and psychospiritual experiences with study personnel after each session.

C: Oral niacin 250 mg, masked to match the intervention, administered during an intervention session that matched the psilocybin arm. During the other session, participants received psilocybin.

O: No primary outcome was specified; psychological measures included changes and differences in changes from baseline 5-Dimension Altered States of Consciousness (5D-ASC), Beck Depression Inventory (BDI), Profile of Mood States (POMS), State-Trait Anxiety Inventory (STAI), and Brief Psychiatric Rating Scale (BPRS). Safety outcomes were blood pressure, heart rate, and arrhythmias.

T: Outcomes measured the day before, the day after, and 2 weeks after each session, and then at monthly intervals for 6 months.

S: Randomized, double-blind (participants + staff), single-site (US), active placebo-controlled, within-participant (ie, patients were their own control) pilot trial. The order of receiving the interventions (psilocybin-first or niacin-first) was randomized, and each patient served as their own control.

Primary conclusion(s): Significant between-group differences in improvement from baseline were observed for psilocybin versus control within the oceanic boundlessness ($P < 0.001$), visionary deconstructuralization ($P < 0.001$), anxious ego dissolution ($P = 0.049$), and auditory alterations ($P = 0.03$) domains of 5D-ACS at unspecified time points using 1-way ANOVA. Differences from baseline BDI reached significance at 6 months ($P = 0.03$), many months after all patients had received both treatment sessions. Similarly, significant differences from baseline STAI-Trait (but not STAI-state) scores were observed at 1 month ($P = 0.001$) and 3 months ($P = 0.03$) after the second session, when all participants had received psilocybin. Nevertheless, authors reported non-significant “trends” for a reduction in POMS and BDI scores from baseline to 2 weeks after psilocybin treatment that was not observed with niacin. Psilocybin was associated with a small statistically significant elevation in heart rate ($P = 0.03$), systolic blood pressure ($P < 0.001$), and diastolic blood pressure ($P = 0.03$) versus control.

Limitations (per authors): Subjects and staff were consistently able to unmask randomized treatments; variable number of contacts with staff; many comparisons were made without differentiating between subjects who had versus had not yet received the intervention previously (ie, each patient’s outcomes following the intervention were compared to the same measures following the control, regardless the ordering of those sessions), and pilot study with small sample size[4]

1.0 Psilocybin for Alcohol Use Disorder

34. Amegadzie S, Mennenga S, Podrebarac S, Duane H, Ross S, Bogenschutz M. Psilocybin-assisted treatment for alcohol use disorder: A clinical perspective. *American Journal on Addictions*. 2018;27(4):317.

NCT not reported.

*It is published as an abstract, so we were unable to verify all inclusion criteria. Bogenschutz et al. 2018⁷³ may be a full-text for this abstract. The investigators mentioned designing **this ongoing trial** using results of a single-arm (uncontrolled) clinical trial of psilocybin for alcohol use disorder by Bogenschutz et al. 2015⁷⁴ (NCT02061293).*

P: People with alcohol use disorder (target enrolled $n = 180$)

I: Psilocybin-assisted therapy, 2-3 sessions. Therapy is Motivational Enhancement and Taking Action (META) therapy, including preparatory, experimental drug-administration, and debrief sessions.

C: Active-control containing diphenhydramine with therapy matching the psilocybin arm.

O: Not specified

T: Not specified, but the trial is planning for a 42 week treatment course

S: Descriptive study of an *ongoing* (ie, incomplete at the time of publishing this abstract) double-blinded, controlled trial.

Primary result(s): Describes experiences from 3 participants in the trial (this is descriptive, and inferences about the possible role of psilocybin cannot be made). Positive experiences were reported including reduced heavy drinking and alcohol abstinence in 2/3 participants.

Limitations (per authors): Preliminary descriptive data that precludes inferences about the efficacy of psilocybin for alcohol use disorder.

LSD Studies

LSD for Anxiety Associated with Life-Threatening Illness

Citations addressing the original phase 2 trial: Gasser et al. 2014 (NCT00920387)

35. Gasser P, Holstein D, Michel Y, et al. Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *The Journal of nervous and mental disease*. 2014;202(7):513-520.

P: Adults with anxiety (STAI trait- or state-scale score ≥ 40) related to life-threatening disease. Half of participants also met criteria for generalized anxiety disorder. Participants discontinued depression and anxiety treatments before the start of the trial.

(Total n randomized = 12; 11 received the intervention)

I: Two psychotherapy-assisted administration sessions of 200 mcg of LSD separated from one another by 2-3 weeks in addition to ongoing drug-free psychotherapy sessions including 3 drug-free psychotherapy sessions lasting 60-90 minutes after each administration session.

C: Two psychotherapy-assisted sessions of 20 mcg LSD (active placebo) separated by 2-3 weeks with 3 drug-free psychotherapy sessions after each administration session.

O: Change in self-reported anxiety symptoms (STAI Form X)

T: Outcome measurements were completed at baseline, 1 week after each LSD-assisted session, and 2 and 12 months after completion of the last LSD-assisted session.

S: Phase 2, randomized (2 LSD 200 mcg: 1 LSD 20 mcg), double-blind, active placebo-controlled, pilot trial. After unmasking, there was an optional open-label crossover period where control participants received 2 LSD (200 mcg)-assisted therapy sessions plus 5 non-drug therapy sessions.

Primary Conclusions: STAI-*state* scores significantly decreased from baseline to 2 months after the 2nd LSD session for active-dose LSD-treated participants compared to control participants (mean [SD] STAI-*state* score at baseline: LSD 200 mcg, 53.1 [4.7] vs control, 47.7 [7.7]; mean [SD] STAI-*state* score at 2-month follow-up: LSD 200 mcg, 41.5 [3.2] vs control, 51.7 [5.3]; $P = 0.021$ for between group difference; effect size [Cohen's d] = 1.2). There were numerical decreases in STAI-*trait* scores between baseline and 2 months after the 2nd LSD session for LSD compared to control; however, this was not statistically significant at the multiplicity-adjusted alpha threshold of 0.025 (mean [SD] STAI-*trait* score at baseline: LSD 200 mcg, 53.2 [4.3] vs control, 43.3 [7.0]; mean [SD] STAI-*state* score at 2-month follow-up: LSD 200 mcg, 45.2 [3.7] vs control, 49.0 [6.1]; $P = 0.033$ for between group difference; effect size [Cohen's d] = 1.1). Anxiety symptom changes were sustained at 12 months in the overall cohort (ie, after LSD 200 mcg-assisted therapy for all participants). No severe LSD-related ADE were reported. In general, a greater variety and higher overall incidence of ADE were reported for the LSD 200 mcg arm, but the majority of events were transient, occurring within 1 day of receipt of LSD.

Limitations (per authors): Small sample size; blinding was insufficient as nearly all participants and therapists successfully identified the group assignment; inability to account for the possible psychological impact of changes in the participants life-threatening disease; assessed quality-of-life secondary outcome measures are focused on physical but not psychological changes.

36. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects. *Journal of psychopharmacology*. 2015;29(1):57-68.

P: Adults with anxiety symptoms associated with life-threatening illness, refer to Gasser et al. 2014.

($n=12$ participants completed the original trial, and $n=10$ entered the long-term follow-up [LTFU] period; data for 9 participants was included for the STAI analysis and audio recording).

I/C: See Gasser et al. 2014. Control participants that did not opt to crossover to the 200 mcg LSD dose after completion of initial study were not eligible for LTFU.

O: Change in self-reported anxiety symptoms (per Spielberger STAI Form X)

T: LTFU, 12 months after last administration of 200 mcg LSD dose

S: Open-label, single-arm LTFU of phase 2 randomized, active-controlled pilot trial, including a qualitative content analysis via semi-structured interviews of participants.

Primary Conclusions: In the total cohort of participants that received 2 LSD (200 mcg)-assisted sessions, there were statistically significant reductions between baseline and 12-months for the mean STAI State score ($P=0.0005$) and STAI Trait score ($p=0.004$). Interviewed participants exhibited a positive impression of LSD-assisted therapy: "...participants consistently reported insightful, cathartic and interpersonal experiences, accompanied by a reduction in anxiety (77.8%) and a rise in quality of life (66.7%)."⁷⁵ Investigators speculate at the potential therapeutic mechanism for LSD-assisted therapy. Participants did not any report adverse events during the extended follow-up.

Limitations (per authors): Refer to limitations mentioned by Gasser et al. 2014; at LTFU, only a subset of the original trial cohort was included; a control group for LTFU was lacking due to cross-over of the control group during the original trial.

Other LSD Citations

37. Liechti ME, Holze F, Vizeli P, Schmid Y. Acute effects of LSD in healthy subjects and in patients during LSD-assisted psychotherapy. *Psychotherapy and Psychosomatics*. 2019;88:75.

NCT not reported

Published as an abstract only, so we are unable to fully confirm that this study meets inclusion criteria.

P: Mix of participants considered healthy and affected by a psychiatric disorder (Total n unclear; the abstract mentions 40 healthy participants, 8 patients with varying unspecified, psychiatric conditions, and 11 patients with life-threatening illness-associated anxiety).

I: LSD 0.1 to 0.2 mg

C: Placebo

O: Changes in visual analog scale scores on the 5-dimensions of Altered States of Consciousness (5D-ASC) scale scores, and mystical experience questionnaire (MEQ)

T: Unspecified, "acute effects"

S: Unclear; appears to be a pooled secondary analysis from 2-3 clinical trials/studies: 1 double-blinded, placebo-controlled cross-over trial of healthy participants; 1 placebo-controlled trial of people with anxiety associated with life-threatening illness; and another of patients treated in psychiatric practices.

Primary conclusion(s): LSD-associated effects measured on the 5D-ASC and MEQ were similar between healthy participants and patients with psychiatric conditions. Among the healthy participants, dose-dependent LSD-associated changes included increased feelings of openness, trust, and closeness; and on the 5D-ASC, increased bliss, insightfulness, and "...changed meaning of percepts"⁷⁶ compared to placebo.

Limitations (per authors): Not reported; information reported in the abstract is insufficient to determine whether all comparisons were versus placebo[5]

Ayahwasca Studies

Ayahwasca for Major Depressive Disorder

Citations addressing the clinical trial: Palhano-Fontes et al. 2019 (NCT02914769)

38. Palhano-Fontes F, Barreto D, Onias H, et al. Rapid antidepressant effects of the psychedelic ayahuasca in treatment-resistant depression: a randomized placebo-controlled trial. *Psychological medicine*. 2019;49(4):655-663.

P: Adults (18-60 years) with treatment-resistant (failure of at least 2 different prior medications) moderate-to-severe (HAM-D score ≥ 17) unipolar major depression. People with prior exposure to ayahuasca were excluded.

(Total n randomized = 35, and 29 were analyzed)

I: Ayahuasca 1 ml/kg made from a single brew (dose of 0.36 mg/kg of N,N-DMT) x 1 dose. Given during an 8-hour session coupled with relaxing music and support of 2 investigators in the next room.

C: Matched (color and contained zinc to stimulate some gastrointestinal distress) liquid placebo 1 ml/kg x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

O: Change in depression severity (on the Hamilton Depression Rating Scale [HAM-D]) from baseline; a secondary outcome was change in Montgomery-Åsberg Depression Rating Scale (MADRS) scores from baseline

T: HAM-D was measured 7 days after the intervention, and MADRS was measured 1, 2, and 7 days after the dose.

S: Randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial

Primary conclusion(s): Ayahuasca-treated participants experienced a significantly larger decrease in mean HAM-D scores between baseline and 7-days post-dose compared to the placebo-treated participants ($P=0.019$; effect size [Cohens d]=0.98). Significant differences in mean MADRS score between the ayahuasca and the placebo arm were observed at day 1, day 2, and day 7 after dosing. At day 7 post-dose, 64% of the ayahuasca arm compared to 27% of the placebo arm were treatment responders.

Limitations (per authors): Small sample size; low generalizability to patients with depression not well represented in the study (patients had treatment-resistant depression with a high comorbidity of a personality disorder); possibility of unmasking interventions. Investigators report taking steps to reduce the possibility of patients or investigators predicting assigned treatments.

39. Galvão-Coelho NL, de Menezes Galvão AC, de Almeida RN, et al. Changes in inflammatory biomarkers are related to the antidepressant effects of Ayahuasca.

Journal of Psychopharmacology. 2020;34(10):1125-1133.

The methods of this article are poorly reported. It seems that they randomized people with or without depression 1:1 to ayahuasca or placebo control, but we are not sure that they stratified by depression diagnosis to achieve a balance between the ayahuasca and control group. The primary exposure reported in this article is depression status.

P: Refer to Palhano-Fontes et al. 2019. This additional analysis included both adults without any psychiatric condition ($n=45$) and adults with treatment-resistant major depression not taking any antidepressants ($N=28$; ayahuasca ($N=14$), placebo ($N=14$)).

I: Ayahuasca 1 ml/kg made from a single brew (dose of 0.36 mg/kg of N,N-DMT) x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

C: Matched (color and contained zinc to stimulate some gastrointestinal distress) liquid placebo 1 ml/kg x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

O: The primary outcome is unclear. Acute changes in blood inflammatory biomarkers (C-reactive protein [CRP] and interleukin [IL]-6) were measured. Additionally, the potential correlation between the inflammatory biomarkers and serum cortisol and serum brain-derived neurotrophic factor (BDNF) was assessed.

T: Timing of biomarker measurement is not explicitly reported. It appears they were measured at baseline pre-treatment (D0-p), and 48 hours after the dosing session (D2).

S: Exploratory analysis of a randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial

Primary conclusion(s): Pre-treatment baseline CRP levels were significantly inversely correlated with cortisol levels among people with depression (*Spearman rho* = -0.40; $P=0.033$), but were not significantly correlated among people without depression ($P=0.28$). Among people with depression, reduced CRP levels from baseline to D2 correlated with a lower MADRS score 48 hours after the intervention among ayahuasca recipients ($P=0.003$ for change in MADRS score from baseline; *Spearman's rho* for correlation=0.57, $P\leq 0.050$), but not placebo recipients ($P>0.050$ for *Spearman's rho*). No significant correlations between treatment arm (ayahuasca vs placebo) and change in IL-6 levels were observed among people with depression.

Limitations (per authors): Use of total BDNF instead of pro-/mature BDNF concentrations; small sample size; population of people with depression is limited to treatment-resistant patients and many of them also had comorbid conditions including an anxiety or personality disorder; limited by use a single treatment with a limited number of blood samples on a given day

40. de Almeida RN, Galvao ACdM, da Silva FS, et al. Modulation of Serum Brain-Derived Neurotrophic Factor by a Single Dose of Ayahuasca: Observation From a Randomized Controlled Trial. *Frontiers in psychology*. 2019;10(101550902):1234.

The methods of this article are poorly reported. It seems that they randomized people with or without depression 1:1 to ayahuasca or placebo control, but we are not sure that they stratified by depression diagnosis to achieve a balance between the ayahuasca and control group. The primary exposure reported in this article is depression status.

P: Refer to Palhano-Fontes et al. 2019. This additional analysis included both adults without depression ($n=45$) and adults with treatment-resistant major depression not taking any antidepressants ($N=28$; ayahuasca ($N=14$), placebo ($N=14$)). People with hypercortisolemia at baseline were excluded from the analysis (4 patients in the healthy population).

I: Ayahuasca 1 ml/kg made from a single brew (dose of 0.36 mg/kg of N,N-DMT) x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

C: Matched (color and contained zinc to stimulate some gastrointestinal distress) liquid placebo 1 ml/kg x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

O: The primary outcome is unclear. Acute changes in serum brain-derived neurotrophic factor (BDNF) levels from baseline were measured. Predictors of baseline serum BDNF were

assessed in a multiple linear regression model. Additionally, changes in BDNF before and after treatment (ayahuasca or placebo) was assessed in a general linear model. A logistic regression model was used to assess depression remission (MADRS score ≤ 10).

T: BDNF and depression severity (MADRS total score) were assessed at baseline before receipt of treatment (D0) and 48 hours after treatment (D2).

S: Randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial

Primary conclusion(s): Among people with depression at baseline, BDNF levels 48 hours after treatment were significantly negatively correlated with MADRS score among people receiving ayahuasca (*Spearman rho* = -0.55 ; $P \leq 0.05$) but not placebo (*Spearman rho* = -0.27 ; $P > 0.05$). Post-treatment BDNF levels were higher among people with or without depression that received ayahuasca compared to those receiving placebo ($P = 0.03$); a between-group difference that was not present at baseline. The authors hypothesize that ayahuasca-induced changes in BDNF may modulate anti-depressant effects.

Limitations (per authors): Not reported. Refer to Palhano-Fontes et al. 2019. Note that this is a small sample size and it unknown whether authors adjusted for multiple statistical comparisons[6].

41. Zeifman RJ, Palhano-Fontes F, Hallak J, Arcoverde E, Maia-Oliveira JP, Araujo DB. The impact of ayahuasca on suicidality: Results from a randomized controlled trial. *Frontiers in Pharmacology*. 2019;10.

P: Adults with unipolar treatment-resistant (insufficient response to 2+ antidepressants) MDD that discontinued antidepressants prior to the trial.
(Total $n = 29$)

I/C: Refer to Palhano-Fontes et al. 2019; single-dose of ayahuasca versus placebo

O: Between-group and within-group effect sizes (Cohen's d) for the change from baseline in mean MADRS-suicidality item score (item 10 rated from 0 to maximum of 6; significant suicidality considered a score ≥ 4) using a fixed-effect linear mixed model controlled for baseline MADRS-suicidality item score

T: Measured at baseline and after (1 day, 2 days, and 7 days) the intervention

S: Secondary analysis of a randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial.

Primary conclusion(s): The effect size (d ; 95% confidence interval) for between-group (ie, ayahuasca versus placebo) changes in suicidality was moderate-sized at day 1 (0.58; -1.32 to 0.17), day 2 (0.56; -1.30 to 0.18) and day 7 (0.67; -1.42 to 0.08) after the receipt of study intervention. The effect size for within-group (ayahuasca recipients) decreases in suicidality

compared to baseline were 1.33, 1.42, and 1.19 at 1 day, 2 days, and 7 days after treatment, respectively. The overall effect for change in suicidality for ayahuasca versus placebo in the linear mixed model was not statistically significant ($P=0.088$); the effect of time, but not the time-intervention interaction, was statistically significant ($P<0.05$).

Limitations (per authors): Lower baseline suicidality scores in the placebo arm, which the investigators tried to control for in the analysis; small study size; low generalizability to people with an immediate risk of suicide; lack of qualitative analysis to improve the understanding of the observed ayahuasca-associated effects; possibility that participants were able to identify which treatment they received.

42. Galvão ACM, de Almeida RN, Silva EAS, et al. Cortisol modulation by ayahuasca in patients with treatment resistant depression and healthy controls. *Frontiers in Psychiatry*. 2018;9.

The methods of this article are poorly reported. It seems that they randomized people with or without depression 1:1 to ayahuasca or placebo control, but we are not sure that they stratified by depression diagnosis to achieve a balance between the ayahuasca and control group. The primary exposure reported in this article is depression status.

P: See Palhano-Fontes et al. 2019. This additional analysis included both adults without depression ($n=43$) and adults with treatment-resistant major depression not taking any antidepressants ($N=28$; ayahuasca ($N=14$), placebo ($N=14$)). People with hypercortisolemia at baseline were excluded from the analysis (4 patients in the healthy population).

I: Ayahuasca 1 ml/kg made from a single brew (dose of 0.36 mg/kg of N,N-DMT) x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

C: Matched (color and contained zinc to stimulate some gastrointestinal distress) liquid placebo 1 ml/kg x 1 dose. Given during an 8-hour dosing session coupled with relaxing music and support of 2 investigators in the next room.

O: The primary outcome is unclear. Acute changes in plasma and awakening salivary cortisol response were measured. Normalized area under the curve (AUC) values for salivary and plasma cortisol, and spearman correlations were calculated.

T: Plasma and awakening (participants slept inpatient the night before) salivary cortisol were measured at baseline pre-treatment (D0-p), during the dosing session (D0-t, about 1 hour and 40 minutes after the dose), and 48 hours after the dosing session (D2).

S: *Exploratory* analysis of a randomized (1:1), double-blind, parallel-group, placebo-controlled single-site (Brazil) trial

Primary conclusion(s): At baseline, after adjustment for sex, people with depression had a lower salivary cortisol response and lower plasma cortisol level relative to healthy

participants. Among people with depression at baseline, salivary cortisol increased significantly ($P=0.03$) more during the ayahuasca dosing session (median % change = 98.72; 25th to 75th quartile=37.89 to 177.16) compared to placebo (median % change = 23.26; 25th to 75th quartile= -5.44 to 41.65). Similar during treatment changes were observed among healthy participants that received ayahuasca relative to placebo. The authors hypothesized that ayahuasca may acutely change salivary cortisol levels.

Limitations (per authors): Not reported. Refer to Palhano-Fontes et al. 2019. Note that this is a small sample size, and it unknown whether authors adjusted for multiple statistical comparisons[7].

Ibogaine Studies

(Nor)Ibogaine for Management of Opioid Withdrawal

43. Glue P, Cape G, Tunnicliff D, et al. Ascending Single-Dose, Double-Blind, Placebo-Controlled Safety Study of Noribogaine in Opioid-Dependent Patients. *Clinical pharmacology in drug development*. 2016;5(6):460-468.

[NCT not reported. The Australian New Zealand Clinical Trial Registry number is ACTRN12613001064796.](#)

P: Adults ages ≥ 18 years discontinuing established methadone opioid substitution therapy (OST) at a dose between 25-80 mg/day, within 7 days after switching to morphine controlled-release x 6 days and immediate release x 1 day

(Total n randomized = 57)

I: One of 3 oral noribogaine doses (60, 120, or 180 mg) administered after fasting ≥ 10 hours and 24 hours after beginning a 72-hour onsite monitoring session

C: Matching placebo administered in onsite session matching the intervention arm

O: No primary outcome was specified; efficacy outcomes were mu-opioid agonist sensitivity, withdrawal (including pupillometry, oximetry, and capnography, time to OST resumption, and opioid withdrawal symptoms using Clinical, Objective and Subjective Opioid Withdrawal Scales [COWS, OOWS, and SOWS]); safety outcomes were change in QTc interval, visual impairment, headache, and nausea

T: All outcomes assessed within 0 to 216 hours after treatment

S: Randomized (2:2:2:1), double-blind, placebo-controlled, parallel-group, single-site (US) trial

Primary conclusion(s): Significant dose- and concentration-dependent increases in the QTc interval (P -values not reported); magnitude of QTc interval prolongation was clinically

meaningful with higher noribogaine doses. Mild and transient adverse effects were common and included visual impairment, headache, and nausea. No significant differences in time-to-resumption of OST or opioid withdrawal symptoms for ibogaine versus placebo; mean (SD) time was 8.6 (3.7), 22.5 (10.3), 11.4 (5.0) and 13.9 (7.4) hours for 60 mg, 120 mg, 180 mg, and placebo, respectively.

Limitations (per authors): This was a single-dose study, but repeated dosing may be required to achieve prolonged withdrawal symptom reduction; study was underpowered for most outcomes.

[1] Urn randomization is a method of generating random assignment while balancing up to 20 baseline characteristics

[2] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

[3] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

[4] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

[5] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

[6] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

[7] Limitation(s) added by writers of this report that were not reported by investigators in the publication.

Appendix G - Phase II evidence review

The following sections summarize findings from Phase 2 of the evidence review organized by topic. Refer to the [full evidence review reports](#) from the DRRC for additional details.

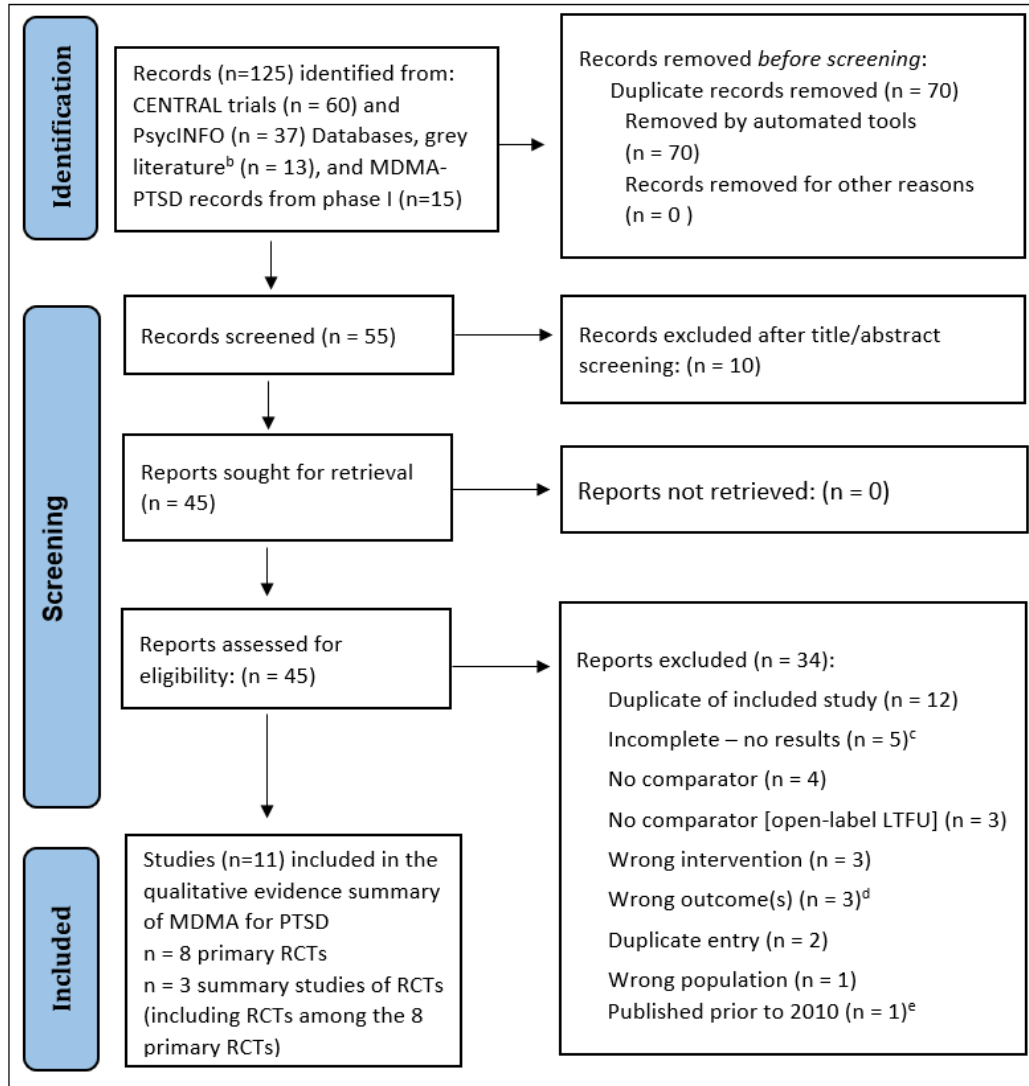
MDMA-assisted therapy for PTSD

Search Results and Description of Included Randomized Controlled Trials

The Phase I report with literature searches in Embase and Medline encompassed 15 records of MDMA for PTSD to bring into screening for the phase II report. The supplemental literature search in CENTRAL, PsycINFO, and MAPS Investigator Brochure (grey literature) identified 110 additional records for screening. Of these, 45 records were moved to full-text records review, from which 11 records met our inclusion criteria. The 11 included records comprise 8 primary RCTs of MDMA for PTSD, and 3 summary studies of various subsets of these RCTs. Altogether, the 8 RCTs (one phase 3 trial and 7 phase 2 trials) randomized 123 participants to active [1] MDMA, and 78 participants to control.⁵⁻¹² These were small trials, with the phase 2 trials ranging from 5-28 enrolled participants⁶⁻¹² and the largest being the phase 3 trial with 91 total participants.⁵

The top 3 most common reasons for exclusion after full-text review were the publication being a duplicate of an included study (n=12), registered trials that are not yet complete (n=5), and studies without a comparator (n=7).

The PRISMA diagram below shows the numbers of records identified, screened, included, and excluded including the primary reason for exclusion.



Abbreviations: LTFU, long-term follow-up; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial

^a Modified from Page et al. 2021²

^b Identified from trials in the 14th Edition (March 2022) of the Multidisciplinary Association for Psychedelic Studies (MAPS) Investigator's Brochure

^c Registered but incomplete trials include NCT04077437 (a second phase 3 trial of MDMA-assisted therapy among people with moderate PTSD severity),³⁹ ACTRN12612000219886 (withdrawn trial),⁷⁷ NCT03752918,⁷⁸ NTR6670,⁷⁹ and NCT04784143 (phase 2 open-label trial comparing 2 versus 3 MDMA-assisted therapy sessions).³⁸

^d A few publications report exploratory, non-PTSD outcomes from included MDMA-assisted therapy trials. Examples of primary outcomes among these studies are eating disorder symptoms,⁸⁰ alcohol or drug use disorder symptoms,⁸¹ and frequency of empathic or ensuic utterances during MDMA-assisted therapy.⁸²

^e One trial appearing to otherwise meet our criteria was published prior to 2010. This was a very small (n=6) trial of women with chronic, treatment-resistant PTSD with a history of sexual assault trauma. They administered escalating MDMA doses (50 mg [n = 3 participants]; 75 mg [n=5 participants) or placebo [n=6 participants]. All participants completed 6 non-drug psychotherapy sessions. Improvements in PTSD symptoms were associated with MDMA; however, a smaller than planned number of participants was enrolled due to political pressure at the site, and thus the study was underpowered to assess the outcomes.⁸³

[1] We use “active MDMA” to refer to MDMA dosages considered to be therapeutic by MAPS investigators. Generally, these are initial MDMA-assisted therapy session dosages ≥ 75 mg. Whereas, initial dosages of MDMA 25-40 mg are referred to as “active placebo” by MAPS investigators, and considered to have no or little therapeutic activity with therapy for the treatment of PTSD.

Summary of Findings

Results from 5 of the 7 included phase 2 trials ($n=99$)^{6-9,12} and 1 phase 3 RCT ($n=91$)⁵ found that 2 or 3 MDMA-assisted therapy sessions, separated by 3-5 weeks and using an oral divided dose of MDMA 80-187.5 mg in combination with 29-40 hours of non-directive manualized therapy, tended to favor or significantly reduced moderate to severe PTSD symptoms after short-term (1-2 month) follow-up. Relative to the control (low-dose ‘inactive’ MDMA or inert placebo with matched psychotherapy), the effect size of MDMA-assisted therapy on the change in PTSD symptoms from baseline to 3-8 weeks after the last dose was large, 0.9 by Cohen’s d , in the phase 3 trial.⁵ Descriptive statistics of clinically important outcomes including the loss of a PTSD diagnosis, PTSD remission, or $\geq 30\%$ improvement in PTSD symptoms also support the short-term efficacy of MDMA-assisted therapy. In the largest phase 3 trial, a higher proportion of active MDMA participants (67%) no longer met PTSD diagnostic criteria 8 weeks after the last MDMA dose than participants receiving inert placebo (32%).⁵ Indirect comparison of effect sizes suggests that MDMA-assisted therapy may be at least similarly effective, or possibly superior, to first-line PTSD therapies including trauma-focused therapy, and possibly better than first-line SSRIs.⁸⁴ However, this should be confirmed by high-quality clinical trials given the potential inaccuracies of comparing the effect of different therapies studied under heterogeneous conditions.

Participants in MDMA-assisted therapy RCTs were adults (mean age around 40 years for many trials) with primarily severe PTSD at baseline.^{5,15} Most participants also suffered from MDD with a high proportion having a *lifetime* history of suicidal ideation (92% in the phase 3 trial), serious ideation (41% in the phase 3 trial), or suicidal behavior (32% in the phase 3 trial).^{5,15} All trials tended to enroll participants that were otherwise healthy, lacking other severe psychiatric illnesses, or severe or uncontrolled medical conditions. Many participants had received at least 1 other treatment for PTSD prior to the trial,^{5,15} suggesting MDMA-assisted therapy may be an effective option for people failing first-line treatments. Trials also enrolled participants with diverse trauma histories,^{5,15} supporting potential use of MDMA-assisted therapy for civilian and veteran populations. In the phase 3 RCT, preliminary evidence from 21% of participants with the difficult-to-treat dissociative PTSD subtype showed that MDMA-assisted therapy was similarly effective for people with and without dissociative PTSD.⁵

Adverse drug effects (ADEs) occurring during RCTs were primarily considered mild to moderate in severity and transient.^{5,15} Common psychiatric events considered to be possibly related to MDMA in the phase 3 trial were bruxism, restlessness, intrusive thoughts, nervousness, and stress.⁵ Similar effects were observed among phase 2 trials, with increased anxiety, difficulty concentrating, jaw clenching, and low mood also occurring numerically more frequently with active MDMA than controls.¹⁵ Common non-psychiatric events occurring more frequently with MDMA were relatively consistent between the phase 3 and phase 2 trials, including but not limited to, gastrointestinal effects (decreased appetite, nausea), muscle tightness, headache, dizziness, perspiration, and cold sensitivity.^{5,15} For most people, MDMA-associated effects resolved within 7 days of MDMA administration.¹⁵

On the days of MDMA administration, transient increases in systolic and diastolic blood pressure and heart rate were observed.^{5,15} These effects occurred consistently between different dosing sessions, and the mean changes returned to baseline by the end of 6-8 hour sessions.¹⁵ MAPS describes the physiologic changes as being no different than the peak effects of moderate intensity exercise for most people.⁸⁵ However, participants with severe cardiovascular disease, which were excluded from MDMA-assisted therapy RCTs,^{5,15} may be more sensitive to these changes, as well as other acute sympathomimetic MDMA effects.

In contrast, participants in the control arms had greater persistence of moderate-severe PTSD symptoms, and more placebo arm participants in the phase 3 trial experienced psychiatric ADEs of anxiety, irritability, nightmares, suicidal ideation, and intentional self-injury than in the MDMA arm.⁵ Reported non-psychiatric events tended to be more frequent with MDMA-assisted therapy, although chills and crying were numerically more frequent in the placebo arm.⁵

Regarding serious adverse events during the RCTs, no deaths were reported per ClinicalTrials.gov,^{10-12,38,86-88} and none of the SAEs occurring in the active MDMA arm during the blinded trial period were considered to be MDMA-related by the investigators.⁶⁻⁹ One SAE of exacerbation of ventricular extrasystole during an open-label MDMA (125 mg) session that resolved after hospitalization for observation with no apparent sequelae was considered possibly MDMA-related.^{6,15} In the phase 3 trial, suicidality was not increased with MDMA (6.5%) compared to placebo (11.4%).⁵ However, the summary study of 6 phase 2 trials found a transient increase in suicidal ideation among people receiving active MDMA versus control. Yet, investigators point out that there was a greater incidence of suicidal ideation among active MDMA participants at baseline, so there is uncertainty about whether the increased suicidal ideation is due to MDMA.¹⁵ The phase 3 trial reported a lack of cases of MDMA abuse.⁵

The risk of bias (ROB) assessment found that none of the 8 RCTs were considered low risk for all factors assessed. Most (62.5%) of the trials were considered high-risk due to potential unblinding of participants and personnel to treatment allocation, as knowledge of treatment allocation could inflate the benefits of MDMA over placebo due to changes in patient or therapist behavior. Trials did attempt to blind participants and therapists, but reports of patient and/or therapist guesses of the assigned allocation suggest that blinding was unsuccessful in many cases. For example, in the phase 3 trial, about 90% of participants correctly guessed their assigned treatment.⁵ Maintenance of blinding is a recognized challenge for clinical trials of psychedelic medications.⁸⁹ Blinding of outcome assessors, which was performed by each RCT, may mitigate bias in the collection of the outcome, but does not eliminate possible bias arising from unblinding of participants and/or personnel.

In addition, 5 of the 8 RCTs were rated as being high risk for attrition bias. In part, this is due to the small sample size of most trials so that attrition of a small number of participants represents $\geq 5\%$ of the entire population. The phase 3 trial was rated as high risk for attrition bias due to missing outcomes. Although the statistical analysis may provide reliable estimates when certain assumptions about the missingness of the data are met, there is uncertainty about whether the assumptions were met. This concern was compounded by discrepancies in the details about handling of the missing outcomes in various analyses conducted and the lack of reported sensitivity analysis about the missing data assumption. Overall, we estimate that if present, attrition bias may overestimate the efficacy of treatment and underestimate possible harms of treatment.

Finally, we noted inconsistent reporting of 1 or more outcomes in 62.5% of the trials, which may indicate selective reporting bias. Although these observations are considered high-risk using our ROB criteria, the impact on the overall efficacy assessment is uncertain. All trials consistently reported the planned primary efficacy outcome (ie, changes in CAPS scores) implying a lack of selectivity for this outcome. Some differences were found in reporting of adverse events between sources (ie, the published journal article versus ClinicalTrials.gov). However, it is possible that some differences could be due to variation in the reporting period or the threshold for the percentage difference between study arms to be included in the publication.

Three small phase 2 RCTs were not published in a journal.¹⁰⁻¹² Thus, results of these trials have not been peer-reviewed. Notably, 2 of the 3 trials were discontinued early after enrolling only a fraction of the planned number of participants.^{10,11} The reason for early discontinuation does not seem to be related to MDMA treatment. One of the discontinued

trials cited personnel turnover as the reason for early termination; on ClinicalTrials.gov, the sponsor notes that the quality of data from this trial cannot be guaranteed.¹⁰

Psilocybin-assisted therapy for major depressive disorder and treatment-resistant depression

Search Results and Description of Included Randomized Controlled Trials

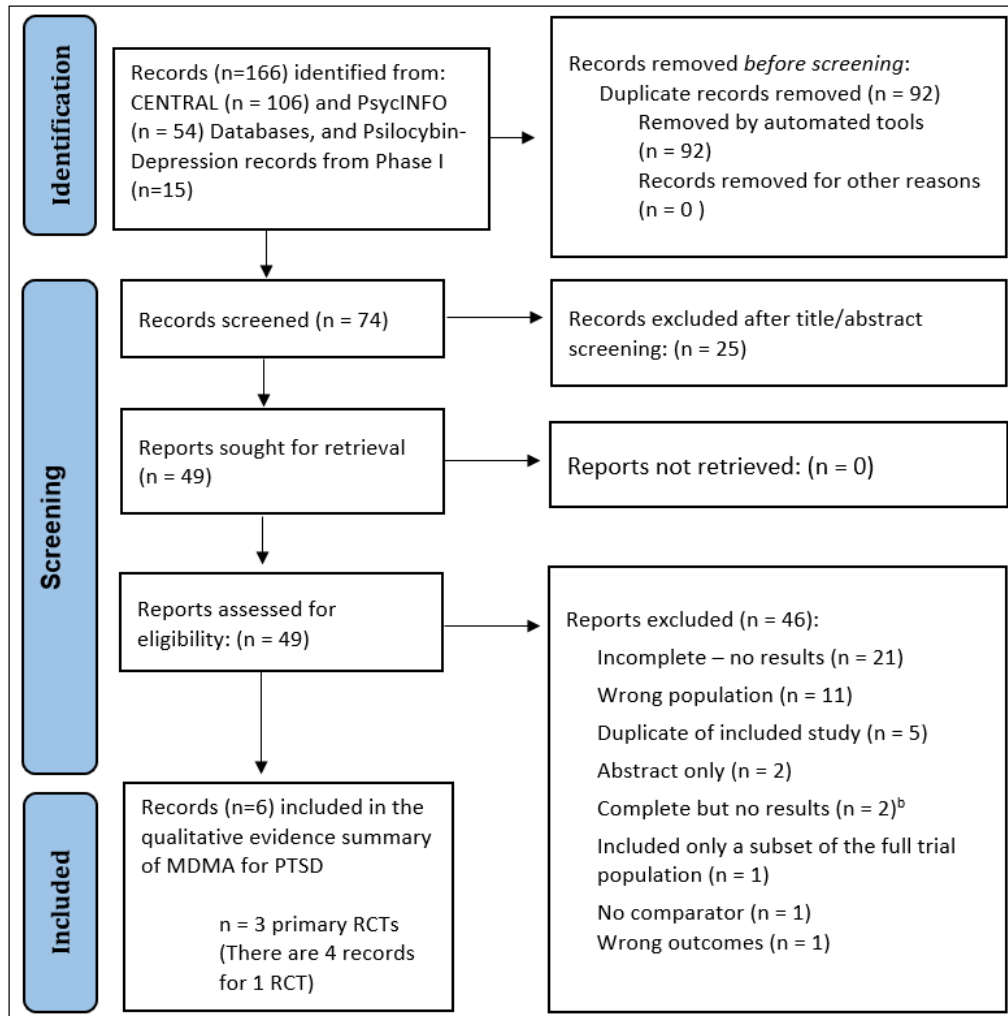
The Phase I report with literature searches in Embase and Medline encompassed 15 records of psilocybin for treatment of depression or psychological distress.⁹³ The supplemental literature search of CENTRAL and PsycINFO identified 151 records. Of these, 49 were moved to full-text records review, from which 6 records pertaining to 3 unique trials met our inclusion criteria.

Two RCTs evaluated psilocybin-assisted therapy for the treatment of moderate-severe MDD.^{16,18} One double-blinded trial (n=59) published by Carhart-Harris et al used a double-dummy design to compare oral psilocybin 25 mg for 2 sessions 3 weeks apart (plus daily placebo capsules for 6 weeks) to active escitalopram 10-20 mg daily for 6 weeks (plus psilocybin 1 mg for 2 sessions 3 weeks apart). Both study arms received psychological support from 2 mental health professionals during preparatory (2 sessions), dosing (2, 4-6 hour sessions), and integration sessions (8 sessions).¹⁶ The second open-label trial (n=27) published by Davis et al compared 2 sessions of oral weight-based psilocybin 20-30 mg/70 kg with supportive psychotherapy (including at least 2 preparatory sessions, 2 8-hour dosing sessions, and 4 integration sessions) to untreated controls (no treatment other than brief weekly phone check-in over an 8 week period) that were randomized to delayed psilocybin treatment. Psychological support was delivered by 2 professionals of varying backgrounds (eg, social work, psychology, or psychiatry).¹⁸

The final trial (n=233) was a triple-blinded RCT that studied psilocybin-assisted therapy for the treatment of TRD (ie, participants with persistent moderate-severe depressive symptoms despite prior adequate trials of 2-4 evidence-based antidepressants). It compared a single dose of 2 different oral psilocybin dosages (10 mg or 25 mg) to the low-dose active comparator, psilocybin 1 mg. Reporting of details for this last trial are limited due to it only being published as posters, but it seems that psilocybin was given with psychological support by a therapist, and also included preparatory and integration sessions.¹⁷

The top 3 reasons for exclusion after full-text review were the record being for an incomplete trial without results (n=21), wrong population (n=11), and being a duplicate of an included study (n=5).

The PRISMA diagram below shows the numbers of records identified, screened, included, and excluded including the primary reason for exclusion.



Abbreviations: LTFU, long-term follow-up; MDMA, 3,4-methylenedioxymethamphetamine; PTSD, post-traumatic stress disorder; RCT, randomized controlled trial

^a Modified from Page et al. 2021²

^b The 2 excluded completed trials were from clinical trial registries. One of these (EUCTR2017-003288-36-NL)⁹⁴ is a duplicate of an included trial (NCT003775200), which has only been published as a poster.¹⁷ The other (NCT03715127) is a phase 2, randomized placebo-controlled trial of a single dose of psilocybin oral capsule (0.215 mg/kg) for treatment of adults (18-60 years old) with mild to moderate MDD.⁹⁵ It was sponsored by the University Zurich. As of October 3, 2022, results have not been posted to ClinicalTrials.gov⁹⁵ and our literature search did not find a full-text publication for it.

Summary of findings

A single small (n=24) randomized controlled trial (RCT) suggested that psilocybin-assisted therapy, as 2 oral doses of psilocybin (20-30 mg/70 kg, 1-3 weeks apart) with psychological support, may be an effective treatment option, at least in the short-term, **for moderate to**

severe unipolar major depressive disorder (MDD) compared to no intervention (ie, wait-list control). This study (Davis et al) reported large effect sizes for change in depression symptoms at week 1 and 4 following the 2nd psilocybin dose (Cohen's *d* for the between group difference at 4 weeks after the 2nd psilocybin dose was 2.6 [95%CI 1.5 to 3.7]).¹⁸ However, since the control group did not receive matched psychological support, it is unclear how much of this effect was due to the psychological support alone.

A second small RCT (n=59, Carhart-Harris et al) among participants with moderate to severe unipolar MDD tended to favor 2 sessions of oral psilocybin 25 mg with psychological support for MDD treatment; but, the effect on the primary endpoint was not superior to a common 1st line antidepressant, daily escitalopram (between group difference at week 6 for the change in depression severity from baseline per the QIDS-SR-16 scale: -2 [95% CI -5 to 0.9]). Descriptively, QIDS-SR-16 response (ie, ≥50% score reduction) was not significantly different between the interventions, but depression remission outcomes suggested a more favorable effect with psilocybin-assisted therapy.¹⁶ Nonetheless, the secondary outcomes of depression response and remission were not adjusted for multiple comparisons, so definitive conclusions cannot be made.

A larger (n=233) phase 2b RCT (Goodwin et al) supports the efficacy of a single oral dose of psilocybin 25 mg in combination with psychological support for the treatment of **moderate to severe treatment-resistant[1] unipolar major depression (TRD)**. Psilocybin 25 mg-assisted therapy was superior to low-dose psilocybin 1 mg-assisted therapy for improving depression symptoms from baseline to 3 weeks after the psilocybin dose (least-squared mean difference on the MADRS scale: -6.6 [95% CI, -10.2 to -2.9]). The moderate psilocybin dose, 10 mg, did not yield a significant effect over low-dose (1 mg) psilocybin. Descriptively, the proportion of participants that responded to treatment, reached remission, and had a sustained response (ie, ≥50% reduction in symptoms by week 3 and maintained to week 12 post-dose without starting an antidepressant) was higher for psilocybin 25 mg versus psilocybin 1 mg.¹⁷ This trial has not been published in a medical journal, so fewer details about its methodology and results are available.

All 3 RCTs tended to enroll a selective population of people with MDD or TRD that were not receiving treatment or were stable to discontinue antidepressants (Davis et al allowed ongoing stable psychotherapy⁹⁶) and were generally at lower risk for adverse events from psilocybin.^{16-18,96,97} The reviewed evidence is most applicable to White adults (mean age in trials was ~40 years old) with a long-standing of depression, moderate to severe depression symptoms, and low suicidality risk.¹⁶⁻¹⁸ In addition, participants lacked conditions that might interfere with development of a participant-facilitator rapport during therapy (eg, some personality disorders), and severe or unstable medical conditions.^{16-18,96,97} Participants with high-risk psychiatric comorbidities (eg, psychotic disorders, active substance dependence)

were also excluded.¹⁶⁻¹⁸ In the trial among participants with TRD, 82% of participants had failed 2 prior drug treatments.¹⁷

Psychological support during each trial was delivered by 2 facilitators/therapists and included non-drug therapy sessions before the dosing sessions (preparation sessions) and after the dosing sessions (integration sessions) in accordance with common psychedelic-assisted therapy approaches.^{16-18,98} Each therapy was described as inner-directed and focused on participant-directed healing with the facilitators available to ensure physical and psychological safety.^{16,18,96-98} During psilocybin dosing sessions for both the Carhart-Harris et al and Davis et al trials, participants laid on a couch/bed with the facilitators nearby while wearing a mask and listening to a pre-selected playlist.^{16,18,96,97} The number of preparation and integration sessions varied by trial. The 2 trials among people with MDD included at least 2 preparation sessions and 4-6 integration sessions.^{16,18,96,97} Similarly, the trial among people with TRD included 3 preparation and 2 integration sessions.¹⁷ Both the Carhart-Harris and Goodwin et al trials based aspects of the therapy on an evidence-based psychotherapy model,^{16,98} but the Davis et al trial provided little detail about the psychological support model.

Regarding safety, no serious adverse events (SADEs) were reported by Carhart-Harris et al or Davis et al.^{16,18,99,100} In the Goodwin et al trial, SADEs tended to occur at a greater frequency with the moderate-high psilocybin doses (10-25 mg) versus the low 1 mg dose. No SADEs occurred on the day of psilocybin dosing. During the entire post-dose period (up to 12 weeks) SADEs were reported among 5 participants (6.3%) in the psilocybin 25 mg arm, 6 participants (8%) in the psilocybin 10 mg arm, and 1 participant (1.3%) in the psilocybin 1 mg arm. During the period between the day after psilocybin dosing to up to 3 weeks later, the number of participants with each SADE were as follows per study arm: 10 mg, 1 hospitalization, 1 intentional self-injury, 2 suicidal ideations; 25 mg: 2 intentional self-injuries and 2 suicidal ideations; 1 mg: no SADEs. Between 3 weeks and 12 weeks after the psilocybin dose, the number of participants were as follows: 10 mg, 1 depression, 1 intentional self-injury, 1 suicidal ideation; 25mg: 1 adjustment disorder, 1 drug withdrawal syndrome, 3 suicidal behaviors; 1 mg: 1 intentional self-injury.¹⁷ Few details about the suicidality events were available; the investigators pointed out that mean suicidality scale risk scores were not increased from baseline for any of the treatment arms, and the 3 suicidal behavior events in the psilocybin 25 mg arm were among people that did not respond to psilocybin-assisted therapy.¹⁷ The other 2 trials used similar doses of psilocybin and did not observe serious suicidality,^{16,18,99,100} but the population of participants may have been at lower risk for suicidal events based on not the majority not having TRD and primarily targeting low-risk participants.^{16,18,96,97} Davis et al reported that suicidal ideation during the trial tended to be low and decline during the trial for both study arms.¹⁸

Details about the comparative incidence of adverse events (ADEs) was limited for the Davis et al trial since authors did not report ADEs in each group during the controlled phase of the study.¹⁸ The incidence of non-serious ADEs on the day of dosing was greater for higher psilocybin doses (ie, 25 mg) compared to low-dose (1 mg) psilocybin in both the Carhart-

Harris et al and Goodwin et al trials.^{16,17} Goodwin et al considered most ADEs to be transient and mild to moderate in severity.¹⁰¹ Both headache and nausea occurred more frequently with high-dose psilocybin versus 1 mg psilocybin on the day of dosing.^{16,17} Other ADEs that appeared to be associated with psilocybin in a dose-dependent manner were dizziness and paresthesia.¹⁷ ADEs persisting after the day of dosing and occurring at a numerically greater frequency with high-dose psilocybin relative to comparator in the Carhart-Harris or Goodwin et al trial included altered mood, anxiety, suicidal ideation, and headache.^{16,17} Few details about vital signs changes were reported; some transient increases in blood pressure and heart rate were observed by Davis et al.¹⁸ Two cases (out of 79) of QT interval prolongation with psilocybin 25 mg occurred in the Goodwin et al trial.¹⁷

Some adverse events were reported more frequently with the comparator treatment relative to moderate-high dose psilocybin treatment after the day of dosing. Psychiatric ADEs occurred at a similar or higher frequency in the daily escitalopram arm (with psilocybin 1 mg) compared to psilocybin 25 mg (with placebo) over 6 weeks.¹⁶ Non-psychiatric ADEs were reported more frequently (difference $\geq 5\%$) with escitalopram compared to psilocybin 25 mg over 6 weeks, including drug mouth, constipation, decreased appetite, fatigue, feeling abnormal, head discomfort, hyperhidrosis, muscle tightness, and asthenia.¹⁶ The incidence of insomnia was numerically greatest in the psilocybin 1 mg arm compared to the moderate-high (10-25 mg) dose arms up to 3 weeks after the psilocybin dosing day.¹⁷

Long-term follow-up for each trial is limited; the trials included 6 to 16 weeks of follow-up.¹⁶⁻¹⁸ Additional descriptive follow-up for 12 months was published for 1 trial (Davis et al) for the entire population that received psilocybin-assisted therapy.¹⁰² This follow-up hinted that responses to 2 doses of psilocybin-assisted therapy may be durable based on a similar response (ie, $\geq 50\%$ reduction in depression severity from baseline) and remission rates at up to 12 months compared to those 1-4 weeks after the psilocybin dose.² However, this analysis was limited by the lack of control group, the risk of confounding due to the one-third of participants starting an antidepressant during the 12 month follow-up, and a limited, observational method for capturing response durability.¹⁰² During the 12-month follow-up, no SADEs were reported; 1 participant (out of 24) reported a single visual perception distortion event 3 months after the 2nd psilocybin dose that was considered possibly psilocybin-related.⁹⁷ The single episode of disturbed visual perception did not meet criteria for Hallucinogen Persisting Perception Disorder (HPPD),¹⁰³ a potential long-term risk of psilocybin use.¹⁰⁴

The domain-based risk of bias assessment found that no trials were rated as low-risk for all domains. The domains with the highest risk ratings were incomplete data (attrition bias) with 2 of 3 trials considered to be high risk^{17,18}; blinding of personnel (1 trial rated as high risk,¹⁸ and others rated as unclear risk^{16,17}); and blinding of participants (subjects), with 2 trials considered to be high risk.^{16,18} The lowest risk domains were blinding of outcome

assessors (2 trials rated as low risk^{17,18}), and use of appropriate allocation sequence generation (2 trials rated as low risk^{16,18}). Selective reporting of outcomes and allocation sequence concealment were also rated as low risk for 1 trial.¹⁶ Two trials were funded by University or crowd/foundation-funded sources, and considered low risk for funding bias.^{16,18} The remaining trial was funded by a for-profit company with an unknown role in the design and conduct of the study.⁶² JADAD scores for the 3 trials were 2 (Davis et al), 3 (Goodwin et al, in part due to limited details being published as a poster only), and 5 (Carhart-Harris et al) out of a maximal score of 5.⁴

Major bias concerns included the risk for unblinding (and lack of blinding in 1 trial¹⁸) of participants and personnel, incomplete outcomes/attrition bias, and lack of standardization of psychological support. Unblinding of participants, among other factors, increased the risk for expectancy bias in each trial (especially Davis et al¹⁸), which tends to be associated with an exaggerated treatment effect. Additionally, 2 trials had the possibility of missing outcomes (ie, attrition) in their primary efficacy analysis.^{17,18} It is unclear if this was adequately addressed by the statistical analysis; if this was not robustly addressed, the treatment effect would also tend to be overestimated,¹⁰⁵ favoring active psilocybin-assisted therapy. In addition, 2 trials (Carhart-Harris et al and Davis et al) reported few details about the training and standardization of psychological support during the trial.^{16,18} The Goodwin et al trial did not report outcomes of training and therapy fidelity monitoring.^{17,101,106-108} Thus, part of the study intervention may have been variably delivered during each trial. It is unclear what effect this might have had on the observed outcome.

[1] Treatment-resistant depression was defined as prior failure of 2–4 evidence-based drug therapies, including augmentation therapy for the same depressive episode that had lasted between 3 months and 2 years.

Appendix H - Training resources

This list of training resources represents the results of a basic search on-line of training resources and does not represent an endorsement of any specific program.

Retrieved September 2022

1. Psychedelic Therapy Training Program - SCPTR (Salt City Psychedelic Therapy & Research) (OL) - <https://www.scptr.org/psychedelic-therapy-training-program->
2. Board of Psychedelic Medicine and Therapies - <https://www.psychedelicsboard.org/>
3. MDMA - MAPS Multidisciplinary Association for Psychedelic Studies - <https://maps.org/2016/01/29/mdma-therapy-training-program/>
4. Psychedelics Fundamentals - MAPS Multidisciplinary Association for Psychedelic Studies - <https://maps.org/psychedelic-fundamentals/>
5. ATMA Journey Centers (OL) <https://www.atmajourney.com/>
6. Berkeley Center for the Science of Psychedelics (Berkeley, CA) <https://bcsp.berkeley.edu>
7. Chacruna (OL and In-person, California) <https://chacruna.net/chacruna-events/>
8. Center For Optimal Living (OL during pandemic, New York) <https://www.centerforoptimalliving.com/trainings-events>
9. Chiron Learning Academy (OL and In-person, Canada)
10. Compass Pathways (OL and interactive) <https://compasspathways.com/our-research/psilocybin-therapy/therapist-training/>
11. Embodied Philosophy (OL and video) <https://www.embodiedphilosophy.org/psychedelic-integration>
12. Healing Realms (OL-San Francisco, CA) <https://www.healingrealmscenter.com/>
13. Innate Path (In-person, Colorado) <https://www.innatepath.org/psychedelic-practice-groups>
14. Ketamine Research Foundation (OL and In-person) <https://ketamineresearchfoundation.org/training/>
15. Microdose/Science of Psychedelics (OL) <https://scienceofpsychedelics.com>
16. Mind Foundation (OL, English and German+ In-person-Germany) <https://mind-foundation.org/apt/>
17. Mind Medicine Australia (OL and In-person, Australia) <https://cpat.mindmedicineaustralia.org>
18. Mindspace Wellbeing/Numinus- (Canada, In-person) <https://www.mindspacewellbeing.com/services/psychedelics/>

19. Network of Emotional Support Teams (NEST) (In-person-California)
https://nestharmreduction.com/avada_portfolio/advanced-harm-reduction-training/
20. People of Color Psychedelic Collective (OL) <https://www.pocpc.org/events>
21. Polaris Insight Center (OL and In-person, California)
22. PRATI (Psychedelic Research and Training Institute, (In-person-Colorado, KAP)
<https://pratigroup.org/trainings/>
23. The Psyched Soul (OL) <https://www.psychedsoul.com/home>
24. Psychedelic Somatic Institute (In-person-Colorado, Australia, Europe)
<https://www.psychedelicomatic.org/psychedelic-psychotherapy-training>
25. Psychedelic Support Accredited Courses (OL, some no-cost)
26. Psychedelics Sitter School (Medicinal Mindfulness) (OL and In-person-Colorado)
<https://psychedelicsittersschool.org/psychedelic-guide-training/>
27. Psychedelics Today (OL) <https://www.psychedeliceducationcenter.com/p/navigating-psychedelics-for-clinicians-and-therapists>
28. Sapience (online and In-person, Massachusetts)
<https://sapiencetherapy.com/research-education-and-training-1>
29. Sage Institute (In-person-California) <https://sageinst.org/kattraining>
30. SoundMind Institute (OL and In-person) <https://soundmind.center/>
31. Synthesis Institute (OL and In-Person-Netherlands)
<https://www.synthesisinstitute.com/psychedelic-practitioner-training>
32. Temenos Center (OL and In-Person, California)
<https://www.temenos.center/ketamine-training-for-professionals>
33. The Ancestor Project (OL) <https://www.theancestorproject.com/psychedelic-liberation-training>
34. The Guiding Presence (OL) <https://theguidingpresence.com>
35. The Ketamine Training Center (In-person-various locations)
<https://theketaminetrainingcenter.com>
36. University of Ottawa: Psychedelics & Spirituality Microprogram (Canada, In-person)
<https://catalogue.uottawa.ca/en/graduate/microprogram-psychedelics-spirituality-studies/#overviewtext>
37. USONA Institute (Reading material and research site-specific In-person)
<https://www.usonainstitute.org/research/#IB>
38. VIU Psychedelic-Assisted Therapy Graduate Certificate Program (Canada, OL)
<https://hhs.viu.ca/psychedelic-assisted-therapy#>
39. Zendo Project (OL, and various locations) <https://zendoproject.org>

40. Psychedelic-Assisted Therapies - California Institute of Integral Studies - <https://www.ciis.edu/research-centers/center-for-psychedelic-therapies-and-research/about-the-certificate-in-psychedelic-assisted-therapies-and-research>
41. Psychedelic-Assisted Therapies - IPI Integrative Psychiatry Institute - <https://psychiatryinstitute.com/ipi-year-long-psychedelic-assisted-therapy-training/>
42. Psychedelic-Assisted Therapies Certificate - Naropa University - <https://www.naropa.edu/academics/extended-campus/psychedelic-assisted-therapies-certificate/>
43. Psychedelic-Assisted Psychotherapy and Integration - Fluence - <https://www.fluencetraining.com/>
44. Psychedelic-Assisted Psychotherapy: The Next Frontier - Harvard University - <https://pll.harvard.edu/course/psychedelic-assisted-psychotherapy-next-frontier?delta=0>
45. The Center for Psychedelic Psychotherapy and Trauma Research - Icahn School of Medicine at Mount Sinai - <https://icahn.mssm.edu/research/center-psychedelic-psychotherapy-trauma-research/training-education>
46. Psychedelic Career Development Pipeline - SSDP Students for Sensible Drug Policy - <https://ssdp.org/our-work/psychedelic-pipeline/>
47. Foundations of Psychedelic Psychotherapy - The Michener Institute of Education at UHN - https://michener.ca/ce_course/fpp/
48. Professional Training in Psychedelic Medicine - The Science of Psychedelics - <https://scienceofpsychedelics.com/>
49. Therapeutic Psilocybin Training Program - TheraPsil - <https://therapsil.ca/training/#>
50. Transdisciplinary Center for Research in Psychoactive Substances - University of Wisconsin-Madison School of Pharmacy - <https://pharmacy.wisc.edu/centers/tcrps>
51. Psychedelic-assisted Therapy - Vancouver Island University - <https://hhs.viu.ca/psychedelic-assisted-therapy>
52. Psychedelic Training - Psychedelic Association of Canada - <https://www.psychedelicassociation.net/resources/education>
53. Psychedelic Integration - Centre of the Heart - <https://courses.centreoftheheart.com/>
54. Certificate Program in Grof Psychedelic Therapy - GROF Legacy Training Canada - <https://program.grof-legacy-training.ca/>
55. Certification Program in Psychedelic Therapy Protocol - Mindsetting Institute - <https://institute.mindsettingpsych.ca/>
56. Navigating Psychedelics Course - Psychedelics Today - <https://psychedelicstoday.teachable.com/p/navigatingpsychedelics>

57. Riding the Wave: Principles of Psychedelic Harm Reduction

<https://offers.psychedellic.support/riding-the-wave-psychedelic-harm-reduction-course/#/>

Appendix I - Ethical and legal considerations of drug-assisted psychotherapy

In approaching its work the Ethical Considerations and Regulation workgroup sought to answer several questions thought to be relevant to the intent of H.B. 167:

1. If the Utah Legislature chooses to allow the use of certain Schedule I substances, what legal and regulatory challenges must Utah government address?
2. How would state authorization of such use be affected by federal law and agencies such as the DEA and FDA?
3. What Utah laws and regulations are required to facilitate use by patients, protect patients, and protect health care providers and others involved in the production, distribution, administration, and use of psychedelic substances?
4. Do models exist for crafting laws and regulations?
5. What happens if Utah institutes a framework for the use of certain psychedelics and one of the authorized Schedule I substances is approved by the FDA for medical use (i.e., rescheduled to CII, II, or IV)?

The following provides additional regulatory considerations and potential models Utah may consider in establishing its framework.

Federal legal considerations

Psychedelic substances are Schedule I Controlled Substances with no currently accepted medical use and a high potential for abuse (e.g., heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, and peyote). See [21 U.S.C. § 812\(c\)\(15\)](#).

Providers and others involved in the system of prescribing and distribution for psychedelics risk action by DEA against their registration or criminal prosecution. For cannabis, the Department of Justice (DOJ) has issued various memoranda describing how it will exercise enforcement discretion in states where certain safeguards are in place. See [DOJ "Ogden Memorandum" Oct. 19, 2009](#); ["Cole Memorandum" June 29, 2011](#); ["Cole II Memorandum" Aug. 29, 2013](#). In addition, budget reconciliation acts have provided that the DOJ cannot use funds to prosecute individuals acting in compliance with state laws. **No such directives currently exist for psychedelic substances.** Banks and landlords have

restrictions because of the status of cannabis as a Schedule I Controlled Substance and such restrictions would apply for psychedelics.

Oregon framework for psilocybin

The Oregon 2020 Ballot Initiative 109 (codified as [Oregon Psilocybin Services Act](#)) was reviewed as an existing model for the clinical use of psychedelic substances. Measure 109 created a program for administering psilocybin products, such as psilocybin-producing mushrooms and fungi, to individuals aged 21 years or older.

Under Measure 109, the Oregon Health Authority (OHA) is responsible for establishing the program and creating regulations for implementation on January 1, 2023. The following regulations are currently included under Measure 109:

- The Oregon Psilocybin Advisory Board (OPAB) advises the OHA.
- Clients will be allowed to purchase, possess, and consume psilocybin at a psilocybin service center and under the supervision of a psilocybin service facilitator after undergoing a preparation session.
- OHA: (i) determines who is eligible to be licensed as a facilitator; (ii) determines what qualifications, education, training, and exams are needed; and (iii) creates a code of professional conduct for facilitators.
- OHA will set psilocybin dosage standards and labeling and packaging rules.
- The initiative authorizes the OHA not to require a client to be diagnosed with or have any particular medical condition to receive psilocybin services.

The Oregon Psilocybin Services Act creates a framework that addresses individuals who provide services surrounding preparation and creating set and setting. However, the Oregon Act does not require individuals to have a mental health condition to obtain psilocybin services and does not require facilitators to be mental health professionals, the Act is not a model for clinical use of psilocybin.

Utah model for medical cannabis

The Utah Medical Cannabis Act (“UMCA”) [Utah Code Ann. §§ 26-61a-101 et seq.](#) was also reviewed as a model and offers lessons learned in the implementation of a medical model for the clinical use of a Schedule I Controlled Substance. See [H.B. 1003](#) 2018 Utah Legislature 3rd Special Session. In general, the UMCA and its rules allow the use of cannabis for designated conditions for individuals who obtain a medical cannabis card based on the recommendation of a medical provider. The following regulations currently govern the UMCA:

- I. **Patient access:** allows an individual with a *qualifying condition* to obtain a medical cannabis patient card on the recommendation of certain medical professionals

- A. Medical cannabis cards are generally allowed for individuals 21 and older for six months; Compassionate Use Board must authorize issuance for 18- to 20-year-olds.
 - B. Access for minors provides for a parent or legal guardian to obtain a medical cannabis guardian card for an eligible minor patient.
 - C. Quantity limits depend on distance from a medical cannabis pharmacy.
- II. **Provider recommendation (not prescribing):** allows physicians, osteopathic physicians, advanced practice registered nurses, and physician assistants to recommend medical cannabis (requires controlled substances license, 4 hours training, and 4 hours training every two years) with limitations on the number of patients for whom the provider recommends treatment.
 - III. **Facilities:** licensing requirements exist for cannabis cultivation facilities, cannabis processing facilities, independent cannabis testing laboratories, and medical cannabis pharmacies, staffed by a Utah pharmacist registered with DHHS.
 - IV. **Security and Testing:** requires security and tracking of medical cannabis and products from cultivation to use to ensure safety and chemical content.
 - V. **Labeling and packaging:** requires certain labeling and childproof packaging.
 - VI. **Electronic Verification:** creates an electronic verification system to facilitate recommendation, dispensing, and record-keeping.
 - VII. **Employment:** provides certain state employment discrimination protection for an individual who lawfully uses medical cannabis.
 - VIII. **Criminal:** establishes criminal penalties for improperly giving or selling medical cannabis.

Further study is required in order to propose more specific regulations the Legislature should consider before Schedule I psychedelic substances can be made legal for treating mental illness in Utah. The UMCA provides a framework for patient access; providers who recommend use; legal protections for employers, patients, and providers; distribution and quality control of products; and facility licensing. However, cannabis providers are not involved with administration of the product as will be required for psychedelic substances used to enhance psychotherapy. Next steps include determining which features of the Utah Cannabis Act and the Oregon Psilocybin Services Act could apply if the Utah Legislature allows use of Schedule I psychedelic products and identifying areas that neither Utah nor Oregon has addressed in its respective legislation.

References

1. Tricco AC, Langlois EV, Straus SE, Alliance for Health P, Systems R, World Health O. *Rapid reviews to strengthen health policy and systems: a practical guide*. World Health Organization; 2017. <https://apps.who.int/iris/handle/10665/258698>
2. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71
3. Page M, Altman D, Egger M. Assessing the Risk of Bias in Randomized Trials. In: Egger M, Higgins J, Smith G, eds. *Systematic Reviews in Health Research: Meta-Analysis in Context*. 3rd ed. BMJ Books; 2022:55-73:chap 4.
4. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12. doi:10.1016/0197-2456(95)00134-4
5. Mitchell JM, Bogenschutz M, Lilienstein A, et al. MDMA-assisted therapy for severe PTSD: a randomized, double-blind, placebo-controlled phase 3 study. *Nat Med*. 2021;27(6):1025-1033. doi:10.1038/s41591-021-01336-3
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8205851/pdf/41591_2021_Article_1336.pdf
6. Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 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. *Lancet Psychiatry*. 2018;5(6):486-497. doi:10.1016/s2215-0366(18)30135-4
7. Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. The safety and efficacy of {+/-}3,4-methylenedioxymethamphetamine-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *Journal of psychopharmacology (Oxford, England)*. 2011;25(4):439-452. doi:<https://dx.doi.org/10.1177/0269881110378371>
8. Oehen P, Traber R, Widmer V, Schnyder U. A randomized, controlled pilot study of MDMA (+/- 3,4-Methylenedioxymethamphetamine)-assisted psychotherapy for treatment of resistant, chronic Post-Traumatic Stress Disorder (PTSD). *Journal of psychopharmacology (Oxford, England)*. 2013;27(1):40-52. doi:<https://dx.doi.org/10.1177/0269881112464827>
<https://journals.sagepub.com/doi/pdf/10.1177/0269881112464827>

9. Ot'alora GM, Grigsby J, Poulter B, et al. 3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial. *J Psychopharmacol*. 2018;32(12):1295-1307. doi:10.1177/0269881118806297
10. Multidisciplinary Association for Psychedelic Studies (MAPS). Randomized Placebo-controlled Study of MDMA-assisted Therapy in People With PTSD - Israel. NCT00402298. ClinicalTrials.gov; 2006. Last Updated July 11, 2022. Accessed September 10, 2022. Available at <https://clinicaltrials.gov/ct2/show/NCT00402298>
11. Multidisciplinary Association for Psychedelic Studies (MAPS). Randomized, Double-Blind, Controlled of MDMA-assisted Psychotherapy in 12 Subjects with PTSD. NCT01958593. ClinicalTrials.gov; 2013. Last Updated July 11, 2022. Accessed September 10, 2022. Available at <https://clinicaltrials.gov/ct2/show/NCT01958593>
12. Multidisciplinary Association for Psychedelic Studies (MAPS). Randomized, Double-blind, Active Placebo-Controlled Pilot Study of MDMA-assisted Psychotherapy in People with Chronic PTSD. NCT01689740. ClinicalTrials.gov; 2012. Last Updated July 6, 2022. Accessed September 10, 2022. Available at <https://clinicaltrials.gov/ct2/show/NCT01689740>
13. Ponte L, Jerome L, Hamilton S, et al. Sleep Quality Improvements After MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder. *Journal of traumatic stress*. 2021;34(4):851-863. doi:<https://dx.doi.org/10.1002/jts.22696>
14. Gorman I, Belser AB, Jerome L, et al. Posttraumatic Growth After MDMA-Assisted Psychotherapy for Posttraumatic Stress Disorder. *Journal of traumatic stress*. 2020;33(2):161-170. doi:<https://dx.doi.org/10.1002/jts.22479>
15. Mithoefer MC, Feduccia AA, Jerome L, et al. 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. *Psychopharmacology*. 2019;236(9):2735-2745. doi:<https://dx.doi.org/10.1007/s00213-019-05249-5>
16. Carhart-Harris R, Giribaldi B, Watts R, et al. Trial of Psilocybin versus Escitalopram for Depression. *The New England journal of medicine*. 2021;384(15):1402-1411. doi:<https://dx.doi.org/10.1056/NEJMoa2032994>
<https://www.nejm.org/doi/pdf/10.1056/NEJMoa2032994?articleTools=true>
17. Goodwin G, Stansfield S, Hellersten D, et al. The safety and efficacy of COMP360 psilocybin therapy in treatment-resistant depression: Results from a phase IIb randomized

controlled trial. Poster presented at: 2022 Annual Meeting of the American Psychiatric Association; May 20-24, 2022; New Orleans, LA.

18. Davis AK, Barrett FS, May DG, et al. Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial. *JAMA psychiatry*. 2021;78(5):481-489. doi:<https://dx.doi.org/10.1001/jamapsychiatry.2020.3285>
19. Lefebvre C, Glanville J, Briscoe S, et al. Technical Supplement to Part 2, Chapter 4: Searching for and selecting studies. In: Higgins J, Thomas J, Chandler J, et al, eds. *Cochrane Handbook for Systematic Reviews of Interventions, version 6.3*. Wiley-Blackwell; 2022:chap 4.S1. Accessed April 7, 2022. Available at www.training.cochrane.org/handbook
20. Higgins J, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.3. The Cochrane Collaboration; 2022. Last Updated February 2022. Accessed April 13, 2022. Available at <https://training.cochrane.org/handbook/current>
21. Glanville J, Dooley G, Wisniewski S, Foxlee R, Noel-Storr A. Development of a search filter to identify reports of controlled clinical trials within CINAHL Plus. *Health Info Libr J*. 2019;36(1):73-90. doi:10.1111/hir.12251
22. Cochrane Library. Cochrane Central Register of Controlled Trials (CENTRAL). CochraneLibrary.com. 2022. Accessed September 7, 2022. Available at <https://www.cochranelibrary.com/central/about-central>
23. Basel Switzerland University Hospital. LSD Therapy for Persons Suffering From Major Depression (LAD). NCT03866252. ClinicalTrials.gov; 2019. Last Updated May, 2022. Accessed May 4, 2022. Available at <https://clinicaltrials.gov/ct2/show/NCT03866252>
24. Basel Switzerland University Hospital. Lysergic Acid Diethylamide (LSD) as Treatment for Cluster Headache. NCT03781128. ClinicalTrials.gov; 2021. Last Updated April 21, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT03781128>
25. Clinicaltrials.gov. Methylenedioxymethamphetamine (MDMA) trials. Clinicaltrials.gov identifier: NCT04158778; NCT02232789; NCT04454684; NCT02427568; NCT00252174; NCT04053036; NCT03752918; NCT05067244; NCT04264026; NCT04968938; NCT03485287; NCT04077437; NCT01958593; NCT02876172; NCT03537014; NCT00353938; NCT01793610; NCT01211405; NCT00090064; NCT00402298; NCT01458327; NCT01689740; NCT04030169; NCT05173831; NCT03282123; NCT04714359; NCT04784143; NCT05138068; NCT02008396; NCT05219175. <https://ClinicalTrials.gov/>. Accessed May 4, 2022. ClinicalTrials.gov; Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/>

26. University Hospital of Basel Switzerland. Pharmacological Interaction Between Doxazosin and Methylenedioxymethamphetamine (MDMA). NCT01386177. ClinicalTrials.gov; 2018. Last Updated December 11, 2018. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT01386177>
27. University Hospital of Basel Switzerland. Pharmacological Interaction Between Carvedilol and Methylenedioxymethamphetamine (MDMA). NCT01270672. ClinicalTrials.gov; 2018. Last Updated December 11, 2018. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT01270672>
28. University Hospital of Basel Switzerland. Pharmacological Interaction Between Clonidine and Methylenedioxymethamphetamine (MDMA). NCT01136278. ClinicalTrials.gov; 2013. Last Updated January 25, 2013. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT01136278>
29. University Hospital of Basel Switzerland. Interaction Between Duloxetine and 3,4-Methylenedioxymethamphetamine (MDMA, Ecstasy). NCT00990067. ClinicalTrials.gov; 2013. Last Updated January 25, 2013. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT00990067>
30. University Hospital of Basel Switzerland. Pharmacological Interaction Between Pindolol and MDMA (3,4-Methylenedioxymethamphetamine). NCT00895804. ClinicalTrials.gov; 2015. Last Updated June 9, 2015. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT00895804>
31. University Hospital of Basel Switzerland. Interaction Between Reboxetine and 3,4-Methylenedioxymethamphetamine: Pharmacodynamics (PD) and Pharmacokinetics (PK). NCT00886886. ClinicalTrials.gov; 2013. Last Updated January 25, 2013. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT00886886>
32. National Institute on Drug Abuse (NIDA). Neurobiology and Pharmacokinetics of Acute MDMA Administration. NCT01148342. ClinicalTrials.gov; 2019. Last Updated December 12, 2019. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT01148342>
33. University of Chicago. Effects of MDMA on Social and Emotional Processing. NCT01849419. ClinicalTrials.gov; 2014. Last Updated December 18, 2014. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT01849419>

34. University of Chicago. Drug Effects on Interpersonal Interaction. NCT05123716. ClinicalTrials.gov; 2021. Last Updated November 17, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT05123716>
35. University Hospital of Basel Switzerland. Effects of MDMA and Methylphenidate on Social Cognition. NCT01616407. ClinicalTrials.gov; 2018. Last Updated December 11, 2018. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT01616407>
36. Multidisciplinary Association for Psychedelic Studies (MAPS). Evaluation of MDMA on Startle Response. NCT03181763. ClinicalTrials.gov; 2022. Last Updated February 21, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT03181763>
37. Basel Switzerland University Hospital. Circulating Oxytocin Changes in Response to the Oxytocin System Stimulator MDMA in Patients With Diabetes Insipidus and Healthy Controls. NCT04648137. ClinicalTrials.gov; 2022. Last Updated April 13, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04648137>
38. Multidisciplinary Association for Psychedelic Studies (MAPS). A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD (MAPP1). NCT03537014. ClinicalTrials.gov; 2021. Last Updated November 11, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/>
39. Multidisciplinary Association for Psychedelic Studies (MAPS). A Multi-Site Phase 3 Study of MDMA-Assisted Psychotherapy for PTSD. NCT04077437. ClinicalTrials.gov; 2021. Last Updated November 3, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04077437>
40. Multidisciplinary Association for Psychedelic Studies (MAPS). A Multi-Site Open-Label Extension Study of MDMA-Assisted Psychotherapy for PTSD. NCT04714359. ClinicalTrials.gov; 2022. Last Updated March 15, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04714359>
41. Multidisciplinary Association for Psychedelic Studies (MAPS). Phase 2 Pilot Safety Study of MDMA-assisted Therapy for Social Anxiety in Autistic Adults. NCT02008396. ClinicalTrials.gov; 2022. Last Updated January 18, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT02008396>
42. Clinicaltrials.gov. Ayahuasca trials. Clinicaltrials.gov identifier: NCT02914769; NCT04711915; NCT04673383. <https://ClinicalTrials.gov/>. Accessed May 4, 2022. ClinicalTrials.gov; Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/>

43. Zurich University Psychiatric Hospital. Neurodynamics of Prosocial Emotional Processing Following Serotonergic Stimulation With N,N-Dimethyltryptamine (DMT) and Harmine in Healthy Subjects. NCT04716335. ClinicalTrials.gov; 2015. Last Updated November 21, 2015. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04716335>
44. Universidade Federal do Rio Grande do Norte. Antidepressant Effects of Ayahuasca: a Randomized Placebo Controlled Trial in Treatment Resistant Depression. NCT02914769. ClinicalTrials.gov; 2017. Last Updated February 17, 2017. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT02914769>
45. Clinicaltrials.gov. Ibogaine trials. Clinicaltrials.gov identifier: NCT04003948; NCT03380728; NCT05029401. <https://ClinicalTrials.gov/>. Accessed June 14, 2022. ClinicalTrials.gov; Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/>
46. Psilocybin trials. Clinicaltrials.gov identifier: NCT05029466; NCT04656301; NCT04661514; NCT04593563; NCT04410913; NCT03866174; NCT03554174; NCT03429075; NCT02061293; NCT04739865; NCT03775200; NCT03715127; NCT03181529; NCT02950467; NCT00957359; NCT00302744; NCT05322954; NCT05243329; NCT05227612; NCT05265546; NCT05242029; NCT05227742; NCT04982796; NCT05042466; NCT04882839; NCT05220046; NCT04754061; NCT04718792; NCT05259943; NCT04989972; NCT05220410; NCT05163496; NCT05065294; NCT04932434; NCT04950608; NCT04959253; NCT05035927; NCT04905121; NCT04620759; NCT04670081; NCT04630964; NCT04522804; NCT04505189; NCT04433845; NCT04433858; NCT04161066; NCT04141501; NCT04123314; NCT04052568; NCT05312151; NCT03356483; NCT03300947; NCT02037126; NCT01943994; NCT03380442; NCT01534494; NCT00979693; NCT04424225. ClinicalTrials.gov; Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/>
47. University of California - San Francisco. Psilocybin Therapy for Chronic Low Back Pain. NCT05351541. ClinicalTrials.gov; 2022. Last Updated May 4, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT05351541>
48. University of California - San Diego. Psilocybin-assisted Therapy for Phantom Limb Pain. NCT05224336. ClinicalTrials.gov; 2022. Last Updated February 4, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT05224336>
49. University of Alabama at Birmingham. Psilocybin-facilitated Treatment for Chronic Pain. NCT05068791. ClinicalTrials.gov; 2022. Last Updated April 1, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT05068791>

50. TRYP Therapeutics. Open-label Study to Assess the Safety and Efficacy of TRP-8802 With Psychotherapy in Adult Participants With Fibromyalgia. NCT05128162. ClinicalTrials.gov; 2021. Last Updated November 19, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT05128162>
51. Yale University. Psilocybin for the Treatment of Migraine Headache. NCT03341689. ClinicalTrials.gov; 2022. Last Updated February 25, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT03341689>
52. Yale University. Psilocybin for the Treatment of Cluster Headache. NCT02981173. ClinicalTrials.gov; 2021. Last Updated September 13, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT02981173>
53. Yale University. Repeat Dosing of Psilocybin in Migraine Headache. NCT04218539. ClinicalTrials.gov; 2021. Last Updated October 25, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04218539>
54. Yale University. Effects of Psilocybin in Concussion Headache. NCT03806985. ClinicalTrials.gov; 2021. Last Updated August 9, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT03806985>
55. Gitte Moos Knudsen. Prophylactic Effects of Psilocybin on Chronic Cluster Headache. NCT04280055. ClinicalTrials.gov; 2021. Last Updated February 20, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04280055>
56. Johns Hopkins University. Effects of Psilocybin in Post-Treatment Lyme Disease. NCT05305105. ClinicalTrials.gov; 2022. Last Updated May 3, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT05305105>
57. NYU Langone Health. The Effects of Psilocybin-Facilitated Experience on the Psychology and Effectiveness of Religious Professionals. NCT02421263. ClinicalTrials.gov; 2022. Last Updated February 14, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT02421263>
58. Johns Hopkins University. Psychopharmacology of Psilocybin in Cancer Patients. NCT00465595. ClinicalTrials.gov; 2019. Last Updated July 18, 2019. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT00465595>
59. Sheppard Pratt Health System. The Safety and Efficacy of Psilocybin in Participants With Type 2 Bipolar Disorder (BP-II) Depression. NCT04433845. ClinicalTrials.gov; 2021. Last

Updated November 1, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04433845>

60. University of California - San Francisco. Psilocybin Therapy for Depression in Bipolar II Disorder. NCT05065294. ClinicalTrials.gov; 2022. Last Updated February 1, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT05065294>

61. COMPASS Pathways. The Safety and Efficacy Of Psilocybin as an Adjunctive Therapy in Participants With Treatment Resistant Depression. NCT04739865. ClinicalTrials.gov; 2022. Last Updated January 26, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04739865>

62. COMPASS Pathways. The Safety and Efficacy of Psilocybin in Participants With Treatment Resistant Depression. NCT03775200. ClinicalTrials.gov; 2022. Last Updated January 26, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT03775200>

63. Dana-Farber Cancer Institute. Pilot Study of Psilocybin-Assisted Therapy for Demoralization in Patients Receiving Hospice Care. NCT04950608. ClinicalTrials.gov; 2022. Last Updated March 29, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT04950608>

64. University of California - San Francisco. Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors. NCT02950467. ClinicalTrials.gov; 2021. Last Updated January 7, 2021. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT02950467>

65. Halucenex Life Sciences Inc. Investigating the Therapeutic Effects of Psilocybin in Treatment-Resistant Post-Traumatic Stress Disorder. NCT05243329. ClinicalTrials.gov; 2022. Last Updated March 15, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT05243329>

66. Strous JFM. [Psilocybin compared with escitalopram for depression]. *Nederlands tijdschrift voor geneeskunde*. 2022;166(nuk, 0400770)

67. Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 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. *The lancet Psychiatry*. 2018;5(6):486-497. doi:[https://dx.doi.org/10.1016/S2215-0366\(18\)30135-4](https://dx.doi.org/10.1016/S2215-0366(18)30135-4)

68. Barone W, Beck J, Mitsunaga-Whitten M, Perl P. Perceived Benefits of MDMA-Assisted Psychotherapy beyond Symptom Reduction: Qualitative Follow-Up Study of a Clinical Trial for Individuals with Treatment-Resistant PTSD. *J Psychoactive Drugs*. 2019;51(2):199-208. doi:10.1080/02791072.2019.1580805
69. Jerome L, Feduccia AA, Wang JB, et al. Long-term follow-up outcomes of MDMA-assisted psychotherapy for treatment of PTSD: a longitudinal pooled analysis of six phase 2 trials. *Psychopharmacology*. 2020;237(8):2485-2497. doi:<https://dx.doi.org/10.1007/s00213-020-05548-2>
70. Danforth AL, Grob CS, Struble C, et al. Reduction in social anxiety after MDMA-assisted psychotherapy with autistic adults: a randomized, double-blind, placebo-controlled pilot study. *Psychopharmacology*. 2018;235(11):3137-3148. doi:<https://dx.doi.org/10.1007/s00213-018-5010-9>
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6208958/pdf/213_2018_Article_5010.pdf
71. Daws RE, Timmermann C, Giribaldi B, et al. Increased global integration in the brain after psilocybin therapy for depression. *Nature medicine*. 2022;28(4):844-851. doi:<https://dx.doi.org/10.1038/s41591-022-01744-z>
<https://www.nature.com/articles/s41591-022-01744-z.pdf>
72. Ross S, Agin-Liebes G, Lo S, et al. Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation Following Psilocybin-Assisted Psychotherapy for Psychiatric and Existential Distress in Life-Threatening Cancer. *ACS pharmacology & translational science*. 2021;4(2):553-562. doi:<https://dx.doi.org/10.1021/acspsci.1c00020>
73. Bogenschutz MP, Podrebarac SK, Duane JH, et al. Clinical Interpretations of Patient Experience in a Trial of Psilocybin-Assisted Psychotherapy for Alcohol Use Disorder. *Front Pharmacol*. 2018;9:100. doi:10.3389/fphar.2018.00100
74. Bogenschutz MP, Forcehimes AA, Pommy JA, Wilcox CE, Barbosa P, Strassman RJ. Psilocybin-assisted treatment for alcohol dependence: A proof-of-concept study. *Journal of Psychopharmacology*. 2015;29(3):289-299. doi:10.1177/0269881114565144
<https://www.embase.com/search/results?subaction=viewrecord&id=L602897394&from=export>
75. Gasser P, Kirchner K, Passie T. LSD-assisted psychotherapy for anxiety associated with a life-threatening disease: a qualitative study of acute and sustained subjective effects.

Journal of psychopharmacology (Oxford, England). 2015;29(1):57-68.

doi:<https://dx.doi.org/10.1177/0269881114555249>

76. Liechti ME, Holze F, Vizeli P, Schmid Y. Acute effects of LSD in healthy subjects and in patients during LSD-assisted psychotherapy. *Psychotherapy and Psychosomatics*. 2019;88:75. doi:10.1159/000502467

<https://www.embase.com/search/results?subaction=viewrecord&id=L629896768&from=export>

77. Psychedelic Research in Science & Medicine Inc. A Randomised, Double-Blind, Active Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Manualised Psychotherapy in Australian War Veterans with Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD) ACTRN12612000219886. WHO.int; 2012. Last Updated January 13, 2020. Accessed September 17, 2022. Available at

<https://trialssearch.who.int/Trial2.aspx?TrialID=ACTRN12612000219886>

78. Yale University. The Effects of MDMA on Prefrontal and Amygdala Activation in PTSD. NCT03752918. ClinicalTrials.gov; 2018. Last Updated February 8, 2022. Accessed September 17, 2022. Available at <https://clinicaltrials.gov/ct2/show/NCT03752918>

79. K.P.C. Kuypers Maastricht University. An open-label, Phase 2 study of the Safety and Effect of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder. NTR6670. WHO.int; 2017. Last Updated May 30, 2022. Accessed September 17, 2022. Available at

<https://trialssearch.who.int/Trial2.aspx?TrialID=NTR6670>

80. Brewerton TD, Wang JB, Lafrance A, et al. MDMA-assisted therapy significantly reduces eating disorder symptoms in a randomized placebo-controlled trial of adults with severe PTSD. *Journal of psychiatric research*. 2022;149(jtj, 0376331):128-135.

doi:<https://dx.doi.org/10.1016/j.jpsychires.2022.03.008>

81. Nicholas CR, Wang JB, Coker A, et al. The effects of MDMA-assisted therapy on alcohol and substance use in a phase 3 trial for treatment of severe PTSD. *Drug Alcohol Depend*. 2022;233:109356. doi:10.1016/j.drugalcdep.2022.109356

82. Corey VR, Pisano VD, Halpern JH. Effects of 3,4-Methylenedioxymethamphetamine on Patient Utterances in a Psychotherapeutic Setting. *The Journal of nervous and mental disease*. 2016;204(7):519-523. doi:<https://dx.doi.org/10.1097/NMD.0000000000000499>

83. Bouso JC, Doblin R, Farré M, Alcázar MA, Gómez-Jarabo G. MDMA-assisted psychotherapy using low doses in a small sample of women with chronic posttraumatic stress disorder. *J Psychoactive Drugs*. 2008;40(3):225-236. doi:10.1080/02791072.2008.10400637 <https://www.tandfonline.com/doi/abs/10.1080/02791072.2008.10400637>
84. Feduccia AA, Jerome L, Yazar-Klosinski B, Emerson A, Mithoefer MC, Doblin R. Breakthrough for trauma treatment: Safety and efficacy of mdma-assisted psychotherapy compared to paroxetine and sertraline. *Frontiers in Psychiatry*. 2019;10doi:10.3389/fpsyt.2019.00650
85. Multidisciplinary Association for Psychedelic Studies (MAPS). *Investigator's Brochure for 3,4-methylenedioxymethamphetamine (MDMA)*. Multidisciplinary Association for Psychedelic Studies (MAPS); 2022: 253 pages. Last Updated March 18, 2022. Accessed August 17, 2022. Available at <https://maps.org/wp-content/uploads/2022/03/MDMA-IB-14th-Edition-FINAL-18MAR2022.pdf>
86. Multidisciplinary Association for Psychedelic Studies (MAPS). Dose-Response Study of MDMA-assisted Psychotherapy in People With PTSD. NCT01793610. ClinicalTrials.gov; 2013. Last Updated July 11, 2022. Accessed September 23, 2022. Available at <https://clinicaltrials.gov/ct2/show/NCT01793610>
87. Multidisciplinary Association for Psychedelic Studies (MAPS). Study Comparing Three Doses of MDMA Along with Therapy in Veterans with Posttraumatic Stress Disorder NCT01211405. ClinicalTrials.gov; 2010. Last Updated July 11, 2022. Accessed September 17, 2022. Available at <https://clinicaltrials.gov/ct2/show/results/NCT01211405>
88. Multidisciplinary Association for Psychedelic Studies (MAPS). MDMA-Assisted Psychotherapy in People With Posttraumatic Stress Disorder. NCT00090064. ClinicalTrials.gov; 2004. Last Updated July 6, 2022. Accessed September 23, 2022. Available at <https://clinicaltrials.gov/ct2/show/NCT00090064>
89. Aday JS, Heifets BD, Pratscher SD, Bradley E, Rosen R, Woolley JD. Great Expectations: recommendations for improving the methodological rigor of psychedelic clinical trials. *Psychopharmacology (Berl)*. 2022;239(6):1989-2010. doi:10.1007/s00213-022-06123-7
90. MAPS Public Benefit Corporation. *A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy*

for the Treatment of Severe Posttraumatic Stress Disorder, Amendment 4 Version 1. Protocol MAPP1, IND #063384. Multidisciplinary Association for Psychedelic Studies (MAPS); 2020: 86 pages. Last Updated May 22, 2022. Accessed September 4, 2022. Available at https://clinicaltrials.gov/ProvidedDocs/14/NCT03537014/Prot_001.pdf

91. Novel PTSD Treatment Advances Toward Regulatory Evaluation with New Collaboration. Press release. Multidisciplinary Association for Psychedelic Studies (MAPS). June 27, 2022. Accessed August 26, 2022. Available at <https://maps.org/2022/06/27/novel-ptsd-treatment-advances-toward-regulatory-evaluation-with-new-collaboration/>

92. Statement: Biden Administration Preparing for Potential FDA Approval of MDMA-Assisted Therapy for PTSD. Press release. Multidisciplinary Association for Psychedelic Studies (MAPS). July 27, 2022. Accessed August 26, 2022. Available at <https://maps.org/2022/07/27/statement-biden-administration-preparing-for-potential-fda-approval-of-mdma-assisted-therapy-for-ptsd/>

93. Drug Regimen Review Center. *Psychotherapy Drugs for the Treatment of Mental Illness: Phase I Evidence Overview*. State of Utah; 2022: 92 pages. Last Updated June 30, 2022. Accessed September 7, 2022. Available at <https://www.utah.gov/pmn/files/868105.pdf>

94. Compass Pathways. The Safety and Efficacy of Psilocybin in Participants with Treatment Resistant Depression (P-TRD). 2017-003288-36. ClinicalTrialsRegister.eu; 2018. Last Updated March 9, 2018. Accessed September 30, 2022. Available at <https://www.clinicaltrialsregister.eu/ctr-search/search?query=2017-003288-36>

95. University of Zurich. Clinical, Neurocognitive, and Emotional Effects of Psilocybin in Depressed Patients - Proof of Concept. NCT03715127. ClinicalTrials.gov; 2022. Last Updated April 29, 2022. Accessed May 4, 2022. Available at <https://ClinicalTrials.gov/show/NCT03715127>