Evidence Brief: Psychedelic Medications for Mental Health and Substance Use Disorders

Supplemental Materials

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APPENDIX A: SEARCH STRATEGY

SYSTEMATIC REVIEWS

Search for current systematic reviews (limited to last 7 years) **Date Searched: 04-26-22**			
A. Bibliographic Databases:	**#**	**Search Statement**	**Results**
MEDLINE: Systematic Reviews Ovid MEDLINE(R) ALL 1946 to April 25, 2022	1	exp Hallucinogens/ad, ae, pd, tu, th, to [Administration & Dosage, Adverse Effects, Pharmacology, Therapeutic Use, Therapy, Toxicity]	17439
	2	(MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic*).ti,ab.	14393
	3	exp Mental Disorders/dt, pc, rh, tu, th [Drug Therapy, Prevention & Control, Rehabilitation, Therapeutic Use, Therapy]	450492
	4	exp Cannabinoids/ or exp Cannabis/	24987
	5	1 or 2	26925
	6	3 and 5	1813
	7	6 not 4	1468
	8	limit 7 to (english language and humans)	1078
	9	(systematic review.ti. or meta-analysis.pt. or meta-analysis.ti. or systematic literature review.ti. or this systematic review.tw. or pooling project.tw. or (systematic review.ti,ab. and review.pt.) or meta synthesis.ti. or meta-analy*.ti. or integrative review.tw. or integrative research review.tw. or rapid review.tw. or umbrella review.tw. or consensus development conference.pt. or practice guideline.pt. or drug class reviews.ti. or cochrane database syst rev.jn. or acp journal club.jn. or health technol assess.jn. or evid rep technol assess summ.jn. or jbi database system rev implement rep.jn. or (clinical guideline and management).tw. or ((evidence based.ti. or evidence-based medicine/ or best practice*.ti. or evidence synthesis.ti,ab.) and (((review.pt. or diseases category/ or behavior.mp.) and behavior mechanisms/) or therapeutics/ or evaluation studies.pt. or validation studies.pt. or guideline.pt. or pmcbook.mp.)) or (((systematic or systematically).tw. or critical.ti,ab. or study selection.tw. or ((predetermined or inclusion) and criteri*).tw. or exclusion criteri*.tw. or main outcome measures.tw. or standard of care.tw. or standards of care.tw.) and ((survey or surveys).ti,ab. or overview*.tw. or review.ti,ab. or reviews.ti,ab. or search*.tw. or handsearch.tw. or analysis.ti. or critique.ti,ab. or appraisal.tw. or (reduction.tw. and (risk/ or risk.tw.) and (death or recurrence).mp.)) and ((literature or articles or publications or publication or bibliography or bibliographies or published).ti,ab. or pooled data.tw. or unpublished.tw. or citation.tw. or citations.tw. or database.ti,ab. or internet.ti,ab. or textbooks.ti,ab. or references.tw. or scales.tw. or papers.tw. or datasets.tw. or trials.ti,ab. or meta-analy*.tw. or (clinical and studies).ti,ab. or treatment outcome/ or treatment outcome.tw. or pmcbook.mp.))) not (letter or newspaper article).pt.	514028
	10	8 AND 9	47

CDSR: Protocols and Reviews EBM Reviews - Cochrane Database of Systematic Reviews 2005 to April 20, 2022	1	hallucinogen*.ti,ab.	1
	2	(MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic*).ti,ab.	7
	3	mental disorder.ti,ab.	16
	4	Cannabinoids or Cannabis.ti,ab.	57
	5	1 or 2	8
	6	3 and 5	0
	7	6 not 4	0
	8	limit 7 to (english language and humans)	0

Search for current systematic reviews (limited to last 7 years) **Date Searched: 04-26-22**		
B. Non-bibliographic databases	**Evidence**	**Results**
AHRQ: evidence reports, technology assessments, U.S Preventative Services Task Force Evidence Synthesis	http://www.ahrq.gov/research/findings/evidence-based-reports/search.html Search: (mental disorders OR substance use) AND (MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic) AHRQ. 2020. Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder: An Update of the PTSD Repository Evidence Base. https://effectivehealthcare.ahrq.gov/products/ptsd-repository-update/protocol AHRQ. 2020. Pharmacologic and Nonpharmacologic Treatments for Posttraumatic Stress Disorder. https://effectivehealthcare.ahrq.gov/products/ptsd-repository-expanded/research	2
CADTH	https://www.cadth.ca Search: (mental disorders OR substance use) AND (MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic) CADTH. 2021. Psychedelic-Assisted Psychotherapy for Post-Traumatic Stress Disorder, Anxiety Disorders, Mood Disorders, or Substance Use Disorders. https://www.cadth.ca/psychedelic-assisted-psychotherapy-post-traumatic-stress-disorder-anxiety-disorders-mood-disorders	1
ECRI Institute	https://guidelines.ecri.org/ Search: (mental disorders OR substance use) AND (MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic)	0

HTA: Health Technology Assessments (UP TO 2016)	http://www.ohsu.edu/xd/education/library/ See CDSR search above	0
EPPI-Centre	http://eppi.ioe.ac.uk/cms/Default.aspx?tabid=62 Use browser search function [CNTL + F] for keyword search Search: MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic	0
NLM	http://www.ncbi.nlm.nih.gov/books Search: (mental disorders OR substance use) AND (MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic)	0
VA Products - VATAP, PBM and HSR&D publications	A. http://www.hsrd.research.va.gov/research/default.cfm Search: (mental disorders OR substance use) AND (MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic)	0

PRIMARY STUDIES

Search for primary literature **Date searched: 04-26-22**		
MEDLINE [Ovid MEDLINE(R) ALL 1946 to April 25, 2022]		
#	**Search Statement**	**Results**
1	exp Hallucinogens/ad, ae, pd, tu, th, to [Administration & Dosage, Adverse Effects, Pharmacology, Therapeutic Use, Therapy, Toxicity]	17439
2	(MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic*).ti,ab.	14393
3	exp Mental Disorders/dt, pc, rh, tu, th [Drug Therapy, Prevention & Control, Rehabilitation, Therapeutic Use, Therapy]	450492
4	exp Cannabinoids/ or exp Cannabis/	24987
5	1 or 2	26925
6	3 and 5	1813
7	6 not 4	1468
8	limit 7 to (english language and humans)	1078
PsycINFO [APA PsycInfo 1806 to April Week 3 2022]		
#	**Search Statement**	**Results**
1	exp Hallucinogenic Drugs/	4238
2	(MDMA or LSD or DMT or ayahuasca or psilocybin or psychedelic*).ti,ab.	6788
3	exp Mental Disorders/	929175
4	exp Cannabinoids/ or exp Cannabis/	15155
5	1 or 2	8737

6	3 and 5	2513
7	6 not 4	2333
8	limit 7 to (english language and humans)	1728

APPENDIX B: EXCLUDED STUDIES

Exclude reasons: 1=Ineligible population, 2=Ineligible intervention, 3=Ineligible comparator, 4=Ineligible outcome, 5=Ineligible timing, 6=Ineligible study design, 7=Ineligible publication type, 8=Outdated or ineligible systematic review, 9=non-English language, 10=unable to retrieve full-text, 11=study published before 1994.

Citation	Exclude Reason
Abramson HA. LSD in psychotherapy and alcoholism. *American Journal of Psychotherapy*. 1966;20(3):415-438.	E7
Abramson HA. Lysergic acid diethylamide (LSD 25). XXXXI. The use of LSD as an adjunct to psychotherapy: fact and fiction. *Journal of Asthma Research*. 1973;10(4):227-235.	E7
Abuzzahab FS, Sr., Anderson BJ. A review of LSD treatment in alcoholism. *International Pharmacopsychiatry*. 1971;6(4):223-235.	E7
Aday JS, Mitzkovitz CM, Bloesch EK, Davoli CC, Davis AK. Long-term effects of psychedelic drugs: A systematic review. *Neuroscience and Biobehavioral Reviews*. 2020;113:179-189.	E8
Agin-Liebes G. The role of self-compassion in psilocybin-assisted motivational enhancement therapy to treat alcohol dependence: A randomized controlled trial. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2021;82(9-B).	E10
Albaugh BJ, Anderson PO. Peyote in the treatment of alcoholism among American Indians. *American Journal of Psychiatry*. 1974;131(11):1247-1250.	E7
Alexander L. Mind and body in biological psychiatry. *Biological Psychiatry*. 1973;5(3):225-238.	E10
Almond K, Allan R. Incorporating MDMA as an adjunct in emotionally focused couples therapy with clients impacted by trauma or PTSD. *The Family Journal*. 2019;27(3):293-299.	E7
Alper KR. Ibogaine: a review. *The Alkaloids Chemistry & Biology*. 2001;56:1-38.	E7
Alper KR, Glick SD. Psychotropic complementary medicines. *British Journal of Psychiatry*. 2006;188:587; author reply 587-588.	E7
Alper KR, Lotsof HS, Frenken GM, Luciano DJ, Bastiaans J. Treatment of acute opioid withdrawal with ibogaine. American Journal on Addictions. 1999;8(3):234-242.	E11
Amoroso T. The Psychopharmacology of +/-3,4 Methylenedioxymethamphetamine and its Role in the Treatment of Posttraumatic Stress Disorder. *Journal of Psychoactive Drugs*. 2015;47(5):337-344.	E7
Amoroso T, Workman M. Treating posttraumatic stress disorder with MDMA-assisted psychotherapy: A preliminary meta-analysis and comparison to prolonged exposure therapy. *Journal of Psychopharmacology*. 2016;30(7):595-600.	E8
Andersen KAA, Carhart-Harris R, Nutt DJ, Erritzoe D. Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatrica Scandinavica*. 2021;143(2):101-118.	E8
Anonymous. LSD: the search for definite conclusions. *JAMA*. 1966;196(4):Suppl:32-33.	E7
Anonymous. Dependence on LSD and other hallucinogenic drugs. *JAMA*. 1967;202(1):141-144.	E7
Anonymous. Preventing misuse of L.S.D. *Lancet*. 1967;1(7483):202.	E7

Citation	Exclude Reason
Anonymous. Control of amphetamines and L.S.D. *Lancet*. 1970;1(7649):708.	E7
Anonymous. L.S.D. in psychiatry. *Lancet*. 1970;2(7678):877-878.	E7
Anonymous. Treatment of alcoholism. II. *Maryland State Medical Journal*. 1973;22(4):17-19.	E7
Anonymous. Think harder about ecstasy. *Nature*. 2004;429(6988):113.	E7
Anonymous. Magic mushroom compound is a potential treatment for patients with major depression. *Nursing Standard*. 2016;30(41):15.	E7
Apud Pelaez IE. Personality Traits in Former Spanish Substance Users Recovered with Ayahuasca. *Journal of Psychoactive Drugs*. 2020;52(3):264-272.	E4
Argento E, Capler R, Thomas G, Lucas P, Tupper KW. Exploring ayahuasca-assisted therapy for addiction: A qualitative analysis of preliminary findings among an Indigenous community in Canada. *Drug & Alcohol Review*. 2019;38(7):781-789.	E6
Argento E, Tupper KW, Socias ME. The tripping point: The potential role of psychedelic-assisted therapy in the response to the opioid crisis. *International Journal of Drug Policy*. 2019;66:80-81.	E7
Avancena ALV, Kahn JG, Marseille E. The Costs and Health Benefits of Expanded Access to MDMA-assisted Therapy for Chronic and Severe PTSD in the USA: A Modeling Study. *Clinical Drug Investigation*. 2022;42(3):243-252.	E6
Averill LA, Abdallah CG. Investigational drugs for assisting psychotherapy for posttraumatic stress disorder (PTSD): emerging approaches and shifting paradigms in the era of psychedelic medicine. *Expert Opinion on Investigational Drugs*. 2022;31(2):133-137.	E7
Bahji A, Forsyth A, Groll D, Hawken ER. Efficacy of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for posttraumatic stress disorder: A systematic review and meta-analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2020;96:109735.	E8
Barabasz-Gembczyk A, Kucia K. Ayahuasca - potential therapeutic properties in psychiatry. Research review. *Psychiatria Polska*. 2020;54(2):381-389.	E7
Barker ET, Buck MF. LSD in a coercive milieu therapy program. *Canadian Psychiatric Association Journal*. 1977;22(6):311-314.	E4
Barnett BS, Greer GR. Psychedelic psychiatry and the consult-liaison psychiatrist: A primer. *Journal of the Academy of Consultation Liaison Psychiatry*. 2021;62(4):460-471.	E7
Barrios AA. An explanation of the behavioral and therapeutic effects of the hallucinogens. *International Journal of Neuropsychiatry*. 1965;1(6):574-592.	E7
Basky G. Policy in focus: Is psilocybin the next cannabis? *CMAJ Canadian Medical Association Journal*. 2021;193(45):E1741-E1742.	E7
Bateman C. Ibogaine may help drug addicts live the 'never again'. *South African Medical Journal Suid-Afrikaanse Tydskrif Vir Geneeskunde*. 2006;96(7):580, 582.	E7
Bedi G. 3,4-Methylenedioxymethamphetamine as a Psychiatric Treatment. *JAMA Psychiatry*. 2018;75(5):419-420.	E7
Bergman RL. Navajo peyote use: its apparent safety. *American Journal of Psychiatry*. 1971;128(6):695-699.	E1
Bienemann B, Ruschel NS, Campos ML, Negreiros MA, Mograbi DC. Self-reported negative outcomes of psilocybin users: A quantitative textual analysis. *PLoS ONE*. 2020;15(2).	E1

Citation	Exclude Reason
Bird CIV, Modlin NL, Rucker JJH. Psilocybin and MDMA for the treatment of trauma-related psychopathology. *International Review of Psychiatry*. 2021;33(3):229-249.	E7
Boer AP, Sipprelle CN. Induced anxiety in the treatment for LSD effects. *Psychotherapy & Psychosomatics*. 1969;17(2):108-113.	E6
Bogenschutz MP, Johnson MW. Classic hallucinogens in the treatment of addictions. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2016;64:250-258.	E7
Bonny HL, Pahnke WN. The use of music in psychedelic (LSD) psychotherapy. *Journal of Music Therapy*. 1972;9(2):64-87.	E7
Bouso JC, Ryan C. Using MDMA in the treatment of post-traumatic stress disorder. *Holland, Julie [Ed] (2001)*. 2001;Ecstasy:The complete guide: A comprehensive look at the risks and benefits of MDMA. (pp. 248-260). x.	E7
Bowen WT, Soskin RA, Chotlos JW. Lysergic acid diethylamide as a variable in the hospital treatment of alcoholism. *Journal of Nervous and Mental Disease*. 1970;150(2):111-118.	E11
Bramble FB. Dependency needs in chronic hallucinogenic drug abusers. *Dissertation Abstracts International*. 1974;34(7-B).	E4
Breeksema JJ, Niemeijer AR, Krediet E, Vermetten E, Schoevers RA. Psychedelic Treatments for Psychiatric Disorders: A Systematic Review and Thematic Synthesis of Patient Experiences in Qualitative Studies. *CNS Drugs*. 2020;34(9):925-946.	E6
Brewerton TD, Lafrance A, Mithoefer MC. The potential use of N-methyl-3,4-methylenedioxyamphetamine (MDMA) assisted psychotherapy in the treatment of eating disorders comorbid with PTSD. *Medical Hypotheses*. 2021;146:110367.	E6
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;149:128-135.	E4
Brown TK, Noller GE, Denenberg JO. Ibogaine and Subjective Experience: Transformative States and Psychopharmacotherapy in the Treatment of Opioid Use Disorder. *Journal of Psychoactive Drugs*. 2019;51(2):155-165.	E4
Bryce JC. An evaluation of LSD in the treatment of chronic alcoholism. *Canadian Psychiatric Association Journal*. 1970;15(1):77-78.	E7
Buckman J. Theoretical aspects of L.S.D. therapy. *International Journal of Social Psychiatry*. 1967;13(2):126-138.	E7
Carbonaro TM, Gatch MB. Neuropharmacology of N,N-dimethyltryptamine. *Brain Research Bulletin*. 2016;126(Pt 1):74-88.	E7
Chabrol H. MDMA assisted psychotherapy found to have a large effect for chronic post-traumatic stress disorder. *Journal of Psychopharmacology*. 2013;27(9):865-866.	E7
Chang AF, Caldwell AB, Moss T. The stability of personality traits in alcoholics during and after treatment as measured by the MMPI: A one year follow-up study. *Proceedings of the Annual Convention of the American Psychological Association*. 1973:389-390.	E11
Check E. Psychedelic drugs: the ups and downs of ecstasy. *Nature*. 2004;429(6988):126-128.	E7
Cheek FE, Osmond H, Sarett M. Observations regarding the use of LSD-25 in the treatment of alcoholism. *Journal of Psychopharmacology*. 1966;1(2):56-74.	E10

Citation	Exclude Reason
Chessick RD, Haertzen CA, Wikler A. Tolerance to LSD-25 in schizophrenic subjects. *Archives of General Psychiatry*. 1964;10(6):653-658.	E4
Chi T, Gold JA. A review of emerging therapeutic potential of psychedelic drugs in the treatment of psychiatric illnesses. *Journal of the Neurological Sciences*. 2020;411:116715.	E7
Cholden LS, Kurland A, Savage C. Clinical reactions and tolerance to LSD in chronic schizophrenia. *Journal of Nervous & Mental Disease*. 1955;122(3):211-221.	E1
Cipriani A, Cowen PJ. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in service personnel. *The Lancet Psychiatry*. 2018;5(6):453-455.	E7
Cline HS, Freeman H. Resistance to lysergic acid in schizophrenic patients. *Psychiatric Quarterly*. 1956;30(4):676-683.	E11
Clyman RC. LSD psychotherapy: a review of the literature and some proposals for future research. *Rhode Island Medical Journal*. 1972;55(9):282-286.	E7
Cohen RS. Adverse symptomatology and suicide associated with the use of methylenedioxymethamphetamine (MDMA; "Ecstasy"). *Biological Psychiatry*. 1996;39(9):819-820.	E1
Corey VR, Pisano VD, Halpern JH. Effects of 3,4-Methylenedioxymethamphetamine on Patient Utterances in a Psychotherapeutic Setting. *Journal of Nervous & Mental Disease*. 2016;204(7):519-523.	E4
Corkery JM. Ibogaine as a treatment for substance misuse: Potential benefits and practical dangers. *Progress in Brain Research*. 2018;242:217-257.	E7
Cox DJ, Garcia-Romeu A, Johnson MW. Predicting changes in substance use following psychedelic experiences: natural language processing of psychedelic session narratives. *American Journal of Drug & Alcohol Abuse*. 2021;47(4):444-454.	E10
Crowley N. A role for psychedelics in psychiatry? *British Journal of Psychiatry*. 2005;187:483; author reply 484-485.	E7
Curran HV, Nutt D, de Wit H. Psychedelics and related drugs: therapeutic possibilities, mechanisms and regulation. *Psychopharmacology*. 2018;235(2):373-375.	E7
Curry AE. Elixir of anguish: The phenomenology of the alcoholic's perennial quest. *Psychiatric Quarterly Supplement*. 1964;38(1):13-20.	E4
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.	E1
Danforth AL, Struble CM, Yazar-Klosinski B, Grob CS. MDMA-assisted therapy: A new treatment model for social anxiety in autistic adults. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2016;64:237-249.	E7
Davey CG. Out of the night-time and into the day: Ketamine and MDMA as therapies for mental disorders. *Australian & New Zealand Journal of Psychiatry*. 2021;55(8):741-743.	E7
Davis AK, Barrett FS, Griffiths RR. Psychological flexibility mediates the relations between acute psychedelic effects and subjective decreases in depression and anxiety. *Journal of Contextual Behavioral Science*. 2020;15:39-45.	E1
Davis AK, Griffiths RR. Errors in a response rate and in effect sizes in study of psilocybin-assisted therapy for major depressive disorder. *JAMA Psychiatry*. 2021;78(5):569.	E7

Citation	Exclude Reason
Davis AK, Renn E, Windham-Herman AM, Polanco M, Barsuglia JP. A Mixed-Method Analysis of Persisting Effects Associated with Positive Outcomes Following Ibogaine Detoxification. *Journal of Psychoactive Drugs*. 2018;50(4):287-297.	E4
Davis AK, So S, Lancelotta R, Barsuglia JP, Griffiths RR. 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) used in a naturalistic group setting is associated with unintended improvements in depression and anxiety. *American Journal of Drug & Alcohol Abuse*. 2019;45(2):161-169.	E1
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.	E4
Day J. The role and reaction of the psychiatrist in LSD therapy. *Journal of Nervous & Mental Disease*. 1957;125(3):437-438.	E7
de Almeida RN, de Menezes Galvao AC, 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.	E4
De Gregorio D, Aguilar-Valles A, Preller KH, et al. Hallucinogens in Mental Health: Preclinical and Clinical Studies on LSD, Psilocybin, MDMA, and Ketamine. *Journal of Neuroscience*. 2021;41(5):891-900.	E7
de Kleine RA, Rothbaum BO, van Minnen A. Pharmacological enhancement of exposure-based treatment in PTSD: A qualitative review. *European Journal of Psychotraumatology*. 2013;4:21626.	E8
de Veen BT, Schellekens AF, Verheij MM, Homberg JR. Psilocybin for treating substance use disorders? *Expert Review of Neurotherapeutics*. 2017;17(2):203-212.	E7
Denber HC. Studies with mescaline. *Rivista di Neurobiologia*. 1964;10(4):Suppl:1157-1168.	E7
Denber HC. Mescaline and lysergic acid diethylamide: therapeutic implications of the drug-induced state. *Diseases of the Nervous System*. 1969;30(2):Suppl:23-27.	E10
Denson R. Dissociative delirium after treatment with lysergide. *Canadian Medical Association Journal*. 1967;97(20):1222-1224.	E6
Denson R. Lysergide therapy and the mauve factor. *Acta Psychiatrica Scandinavica*. 1968;44(3):280-288.	E11
Denson R. Complications of therapy with lysergide. *Canadian Medical Association Journal*. 1969;101(11):53-57.	E11
Denson R, Sydiaha D. A controlled study of LSD treatment in alcoholism and neurosis. *British Journal of Psychiatry*. 1970;116(533):443-445.	E1
Ditman KS, et al. Psychological and drug variables in the LSD experiences of alcoholics. *Psychotherapy and Psychosomatics*. 1967;15(1):15.	E10
DiVito AJ, Leger RF. Psychedelics as an emerging novel intervention in the treatment of substance use disorder: a review. *Molecular Biology Reports*. 2020;47(12):9791-9799.	E7
Dominguez-Clave E, Soler J, Pascual JC, et al. Ayahuasca improves emotion dysregulation in a community sample and in individuals with borderline-like traits. *Psychopharmacology*. 2019;236(2):573-580.	E1
Donnelly JR. The need for ibogaine in drug and alcohol addiction treatment. *Journal of Legal Medicine*. 2011;32(1):93-114.	E7

Citation	Exclude Reason
Dos Santos RG, Balthazar FM, Bouso JC, Hallak JE. The current state of research on ayahuasca: A systematic review of human studies assessing psychiatric symptoms, neuropsychological functioning, and neuroimaging. *Journal of Psychopharmacology*. 2016;30(12):1230-1247.	E1
Dos Santos RG, Bouso JC, Alcazar-Corcoles MA, Hallak JEC. Efficacy, tolerability, and safety of serotonergic psychedelics for the management of mood, anxiety, and substance-use disorders: a systematic review of systematic reviews. *Expert Review of Clinical Pharmacology*. 2018;11(9):889-902.	E8
Dos Santos RG, Hallak JE, Baker G, Dursun S. Hallucinogenic/psychedelic 5HT2A receptor agonists as rapid antidepressant therapeutics: Evidence and mechanisms of action. *Journal of Psychopharmacology*. 2021;35(4):453-458.	E7
Dos Santos RG, Osorio FL, Crippa JA, Hallak JE. Antidepressive and anxiolytic effects of ayahuasca: a systematic literature review of animal and human studies. *Revista Brasileira de Psiquiatria*. 2016;38(1):65-72.	E8
dos Santos RG, Osorio FL, Crippa JAS, Bouso JC, Hallak JEC. The therapeutic potential of ayahuasca and other serotonergic hallucinogens in the treatment of social anxiety. *Osorio, Flavia de Lima [Ed]; Donadon, Mariana Fortunata [Ed] (2018)*. 2018;Social anxiety disorder:Recognition.	E7
Doss MK, Povazan M, Rosenberg MD, et al. Psilocybin therapy increases cognitive and neural flexibility in patients with major depressive disorder. *Transl Psychiatry Psychiatry*. 2021;11(1):574.	E4
Eagle CT. Music and LSD: An empirical study. *Journal of Music Therapy*. 1972;9(1):23-36.	E6
Erritzoe D, Roseman L, Nour MM, et al. Effects of psilocybin therapy on personality structure. *Acta Psychiatrica Scandinavica*. 2018;138(5):368-378.	E4
Fadiman J, Korb S. Might microdosing psychedelics be safe and beneficial? An initial exploration. *Journal of Psychoactive Drugs*. 2019;51(2):118-122.	E6
Faillace LA. Clinical use of psychotomimetic drugs. *Comprehensive Psychiatry*. 1966;7(1):13-20.	E7
Faillace LA, Vourlekis A, Szara S. Clinical evaluation of some hallucinogenic tryptamine derivatives. *Journal of Nervous & Mental Disease*. 1967;145(4):306-313.	E4
Faillace LA, Vourlekis A, Szara S. Hallucinogenic drugs in the treatment of alcoholism: a two-year follow-up. *Comprehensive Psychiatry*. 1970;11(1):51-56.	E11
Fauvel B, Strika-Bruneau L, Piolino P. Changes in self-rumination and self-compassion mediate the effect of psychedelic experiences on decreases in depression, anxiety, and stress. *Psychology of Consciousness: Theory, Research, and Practice*. 2021(Pagination).	E1
Feduccia AA, Jerome L, Mithoefer MC, Holland J. Discontinuation of medications classified as reuptake inhibitors affects treatment response of MDMA-assisted psychotherapy. *Psychopharmacology*. 2021;238(2):581-588.	E4
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;10:650.	E8
Fink M, Simeon J, Haque W, Itil T. Prolonged adverse reactions to LSD in psychotic subjects. *Archives of General Psychiatry*. 1966;15(5):450-454.	E6
Frenken G. From the roots up: ibogaine and addict self-help. *The Alkaloids Chemistry & Biology*. 2001;56:283-292.	E7

Citation	Exclude Reason
Fuentes JJ, Fonseca F, Elices M, Farre M, Torrens M. Therapeutic use of LSD in psychiatry: A systematic review of randomized-controlled clinical trials. *Frontiers in Psychiatry*. 2020;10:943.	E8
Galvao-Coelho NL, Marx W, Gonzalez M, et al. Classic serotonergic psychedelics for mood and depressive symptoms: a meta-analysis of mood disorder patients and healthy participants. *Psychopharmacology*. 2021;238(2):341-354.	E8
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APPENDIX C: EVIDENCE TABLES

CHARACTERISTICS OF INCLUDED PRIMARY STUDIES

RCTs

Author Year **N**	**Psychedelic Medication** ***Follow-up***	**Participant Characteristics**	**Dose** ***Sessions***	**Co-intervention**	**Comparator**	**Medication Discontinued Prior to Intervention?**
Alcohol Use Disorder						
Bogenschutz 2022[1] N=95	Psilocybin *36 weeks*	Mean age: 45.7 % female: 42 % non-Hispanic White: NR	Session 1: 25 mg/kg Session 2: 30-40 mg/kg based on session 1 experience *2 sessions, 8 hours*	12 psychotherapy sessions	Diphenhydramine: 50mg	NR
Major Depressive Disorder						
Carhart-Harris 2021[2] N=59	Psilocybin *6 weeks*	Mean age: 41 % female: 34 % non-Hispanic White: 88	25 mg 3 weeks apart + 6 weeks of daily placebo *2 sessions*	1 preparatory session, 2 dosing sessions, 3 debriefing sessions	Escitalopram	Yes
Davis 2021[3] & Gukasyan 2022[4] N=27	Psilocybin *1 month, 12 months*	Mean age: 40 % female: 67 % non-Hispanic White: 92	Session 1: 20mg/70 kg Session 2: 30mg/70kg *2 sessions*	2 prep meetings (8 hours total) and follow-up (2–3 hours total)	8-week delay group	Yes

Author Year **N**	**Psychedelic Medication** ***Follow-up***	**Participant Characteristics**	**Dose** ***Sessions***	**Co-intervention**	**Comparator**	**Medication Discontinued Prior to Intervention?**
Palhano-Fontes 2019[5] & Zeifman 2019[6] N=29	Ayahuasca *7 days*	Mean age: 42 % female: 72 % non-Hispanic White: 59	1ml/kg ayahuasca containing 0.36mg/kg N, N-DMT *One 8hr session*	None	Placebo (0mg)	Yes
Opioid Use Disorder						
Glue 2016[7] N=27	Ibogaine (Noribogaine) *72 hours + 120 hours, 168, 216 hours after dose*	Mean age: 41 % female: 22 % non-Hispanic White: 74	60mg, 120mg, 180mg (ascending dose) *1 session*	None	Placebo (0mg)	NR
Posttraumatic Stress Disorder						
Bouso 2008[8] [a] N=6	MDMA *12 months*	Mean age: 36 % female: 100 % non-Hispanic White: 0 (100% Spanish)	50 mg-75mg *1 session*	Three 90-min sessions before and after a single 8-hour MDMA session	Placebo	Yes
Mitchell 2021[9] N=90	MDMA *18 weeks after baseline*	Mean age: 41 % female: 66 % non-Hispanic White: 90	80-120mg + 40-60mg supplement *Three 8hr sessions, 4 weeks apart*	Three 90-min preparatory sessions, 3 8-hour MDMA sessions, and 9 90-min integration sessions	Placebo (0mg)	Yes

Author Year **N**	**Psychedelic Medication** ***Follow-up***	**Participant Characteristics**	**Dose** ***Sessions***	**Co-intervention**	**Comparator**	**Medication Discontinued Prior to Intervention?**
Mithoefer 2011[10] & Mithoefer 2013[11] N=20	MDMA *2 months*	Mean age: 40 % female: 85 % non-Hispanic White: 100	125mg + 62.5mg optional supplement *2 experimental sessions 3–5 weeks apart*	Two 90-min preparatory sessions, 2 all-day MDMA sessions and overnight clinic stays, 8 90-min integration sessions	Placebo (0mg)	Yes
Mithoefer 2018[12] N=26	MDMA *1 month after second experimental session*	Mean age: 37 % female: 27 % non-Hispanic White: 85	75mg or 125mg MDMA *Two 8hr sessions*	Two 90-min preparatory sessions, two 8-hour MDMA sessions and overnight clinic stays, six 90-min integration sessions	Active control (30mg)	Yes
Mithoefer 2019[13] [b] N=105	MDMA *1–2 months*	Mean age: 41 % female: 61 % non-Hispanic White: 92	75mg, 100mg, or 125 mg *Two 8hr sessions, 3–5 weeks apart*	Two to three 90-min preparatory sessions, two 8-hour MDMA sessions and overnight clinic stays, and three to four 90-min integration sessions	Active control (0–40mg MDMA)	Yes
Oehen 2013[14] N=12	MDMA *3 weeks, 2 months, 12 months*	Mean age: 41 % female: 83 Race/ethnicity: NR	125mg + 62.5mg supplemental dose *3 sessions, 8hr each*	3 preparatory sessions, three 8-hour MDMA sessions and overnight clinic stays, 12 integration sessions	Active control (25 mg + 12.5mg)	Yes

Author Year **N**	**Psychedelic Medication** ***Follow-up***	**Participant Characteristics**	**Dose** ***Sessions***	**Co-intervention**	**Comparator**	**Medication Discontinued Prior to Intervention?**
Ot'alora 2018[15] N=28	MDMA *1 month*	Mean age: 42 % female: 68 % non-Hispanic White: 93	125 or 100mg *Two 8hr sessions, 1 month apart*	Three 90-min preparatory sessions, two 8-hour MDMA sessions, and 6 integration sessions	Active control (40mg)	Yes
NCT01958593 N=6	MDMA *1 month after second experimental session*	Mean age: 48 % female: 50 % non-Hispanic White: 83	Dose NR *2 sessions*	3 preparatory sessions, 2 MDMA sessions, and 2 integrative therapy sessions	Placebo (0mg)	NR
NCT01689740 N=8	MDMA *1 month after second experimental session*	Mean age: NR % female: 38 % non-Hispanic White: 87	125mg + 62.5mg supplemental dose *Two 6–8hr sessions*	3 preparatory sessions, 2 MDMA sessions, and 2 integration sessions	Active control (25 mg + 12.5mg)	NR
Social Anxiety Disorder						
Dos Santos 2021[16] N=17	Ayahuasca *1 week, 2 weeks, 3 weeks*	Age: 25 % female: 88 Race: NR	2 mL/kg *1 session*	None	Placebo (0mg)	NR

Notes. [a] Bouso 2008 study terminated early due to "political pressure." [b] Mithoefer 2019 is a pooled analysis of Mithoefer 2011, Mithoefer 2018, Oehen 2013, Otalora 2018, NCT0195893, and NCT01689740.
Abbreviations. hr=hour; MDMA=3,4-methylenedioxy-methamphetamine; N, N-DMT=N, N-Dimethyltryptamine; mg=milligram; NR=not reported.

Observational Studies

Author Year ***N***	Psychedelic Medication ***Follow-up***	Participant Characteristics	Dose ***Sessions***	Co-intervention	Medication Tapered Prior to Intervention?
Alcohol Use Disorder					
Bogenschutz 2015[17] N=10	Psilocybin *36 weeks*	Mean age: 40 % female: 40 % non-Hispanic White: 30	Session 1: 0.3 mg/kg Session 2: 0.4 mg/kg dependent on initial experience *2 sessions, 8 hours*	7 sessions of Motivational Enhancement Therapy, 3 preparation sessions, and 2 debriefing sessions	NR
Sessa 2021[18] N=14	MDMA *8 weeks, 3, 6, and 9 months*	Mean age: 48 % female: 43 Race/ethnicity: NR	125mg + 62.5mg booster dose *2 sessions, 6-8 hours*	10 psychotherapy sessions	Yes
Major Depressive Disorder					
Carhart-Harris 2016[19] & 2018[20] N=20	Psilocybin *1 week - 6 months*	Age: 27-64 % female: 70 % non-Hispanic White: 75	10mg, 25 mg *2 sessions, 1 week apart*	None	Yes
Lyons 2018[21 a] N=30	Psilocybin *1 week - 30 days*	Mean age: 42 % female: 27 % non-Hispanic White: 93	10mg, 25 mg (1 week apart) *2 sessions, 1 week apart*	Psychological support consisting of a preparation session and integration sessions led by 2 clinical psychiatrists	Yes
Osorio 2015[22] N=6	Ayahuasca *40 min – 21 days post ingestion*	Mean age: 44 % female: 66 % non-Hispanic White: NR	120-200ml (2.2ml/kg), with 0.8mg/ml DMT and 0.21 mg/ml harmine *1 session, 4 hrs*	None	Yes

Author Year ***N***	**Psychedelic Medication** ***Follow-up***	**Participant Characteristics**	**Dose** ***Sessions***	**Co-intervention**	**Medication Tapered Prior to Intervention?**
Sanches 2016[23] & Zeifman 2021[24] N=17	Ayahuasca *1–21 days after treatment*	Mean age: 42.71 % female: NR % non-Hispanic White: NR	120–200ml (2.2ml/kg), with 0.8mg/ml DMT and 0.21 mg/ml harmine *1 session, 4 hours*	None	Yes
Stroud 2018[25 a] N=17	Psilocybin *1 month*	Mean age:44.94 % female: 47 % non-Hispanic White: NR	10mg 1st dose, 25mg 2nd dose *2 sessions*	Integrative therapy	Yes
Obsessive Compulsive Disorder					
Moreno 2006[26] N=9	Psilocybin *24 hours*	Mean age: 40.9 % female: 22.2 % non-Hispanic White: NR	Varying dose 100ug/kg, 200 ug/kg, or 300 ug/kg with 25 ug/kg dose during 1 of the treatment sessions *4 sessions, 1 week apart, lasting 8 hours*	None	Yes
Opioid Use Disorder					
Brown 2018[27] N=30	Ibogaine *1–12 months*	Mean age: 29 % female: 17 % non-Hispanic White: 90	1540 mg ± 920 mg *NR*	None	Yes
Davis 2017[28] *N=88*	Ibogaine 3 years	Age: 9% 18–24 years old, 41% 25–34 years old, 39% 35–54 years old, 10% 55+ years old % female: 27 % non-Hispanic White: 89	10–20mg/kg *1 session*	Participation in detoxification program	Yes

Author Year ***N***	**Psychedelic Medication** ***Follow-up***	**Participant Characteristics**	**Dose** ***Sessions***	**Co-intervention**	**Medication Tapered Prior to Intervention?**
Knuijver 2022[29] N=14	Ibogaine *2–24 hours after treatment*	Age (median): 48 % female: 14 % non-Hispanic White: NR	10mg/kg *1 session*	None	Yes
Malcolm 2018[30] N=50	Ibogaine *24 and 48 hours*	Mean age: 31 % female: 39 % non-Hispanic White: 78	18–20mg/kg *1 session*	3-part treatment program: coaching, medical screening, detoxification treatment, optional residential aftercare program	Yes
Noller 2018[31] N=14	Ibogaine *12 months*	Mean age: 38 % female: 50 % non-Hispanic White: 100	25–55 mg/kg (mean 31.4, SD 7.6) *1 session*	Diazepam 5–30mg and zopiclone 7.5–15mg	NR
Posttraumatic Stress Disorder					
Jardim 2021[32] N=3	MDMA *2 months*	Mean age: 40 % female: 67 % non-Hispanic White: 67	Session 1 :112.5mg Sessions 2–3: 187.5mg *3 sessions, 8 hours*	Three 90-min preparatory sessions, three 8-hour MDMA sessions, and nine 90-min integrative therapy sessions	Yes
Monson 2020[33] N=12	MDMA *3- and 6-months post-treatment*	Mean age: 47 % female: 40 % non-Hispanic White: 100	75mg 1st session, 100mg 2nd session *2 sessions*	5 preparatory CBCT sessions, 2 MDMA 6-8 hour MDMA sessions, two 1.25-hour integration sessions, 8 post MDMA CBCT sessions	Yes

Author Year ***N***	**Psychedelic Medication** ***Follow-up***	**Participant Characteristics**	**Dose** ***Sessions***	**Co-intervention**	**Medication Tapered Prior to Intervention?**
Wang 2021[34] N=37	MDMA *18 weeks after baseline*	Mean age: 36 % female: 60 % White: 73 % not Hispanic/Latino: 94.6	80–100mg + 40–50mg supplement 1st session, 120–25mg + 60–62.5mg supplement 2nd and 3rd session *Three 6-8 hour sessions, 3-5 weeks apart*	3 preparatory sessions, three 6–8-hour MDMA sessions and overnight clinic stays, and 9 integration sessions	Yes
Substance Use Disorder					
Thomas 2013[35] N=12	Ayahuasca *6 months*	NR	Dose NR *2 sessions*	Participation in 4-day "Working with Addiction and Stress" retreats	NR
Mash 2000[36] N=27	Ibogaine *1 month*	Mean age: 35 for opioid group, 38 for cocaine group % female: 17 % non-Hispanic White: NR	500, 600, or 800mg *1 session*	Participation in inpatient detoxification program	NR
Mash 2001[37] N=32	Ibogaine *36 hours–10 days*	Mean age: 34 % female: 31 % non-Hispanic White: 82	800 mg *1 dosing session*	NR	NR
Mash 2018[38] N=191	Ibogaine *1 month*	Mean age: 35.9 % female: 24.6 % non-Hispanic White: 87.4	8–12 mg/kg *1 dosing session*	Psychological support	NR

Author Year ***N***	**Psychedelic Medication** ***Follow-up***	**Participant Characteristics**	**Dose** ***Sessions***	**Co-intervention**	**Medication Tapered Prior to Intervention?**
Schenberg 2014[39] N=75	Ibogaine *NR*	Mean age: NR % female: 11 % non-Hispanic White: NR	7.5–20mg/kg *1–9 sessions, 1 dosing session with optional additional sessions as appropriate*	Psychological therapy	NR
Tobacco Use					
Johnson 2014[40] & 2017[41] N=15	Psilocybin 6 months	Mean age: 51 % female: 33.3 % non-Hispanic White: 93%	Moderate dose: 20mg/70kg High dose: 30mg/70kg *2–3 sessions*	CBT	NR
Other Mental Health Diagnoses[b]					
Davis 2020[42] N=51	Ibogaine, 5-MeO-DMT *1 month–2 years*	Mean age: 40 % female: 4 % non-Hispanic White: 92%	Ibogaine: 10mg/kg MeO-DMT: 50mg *2 sessions (1 ibogaine, 1 MeO-DMT), 3 days of treatment*	Group therapy, psychological support	Yes

Notes. [a] Lyons 2018 and Stroud 2018 included comparison groups to "healthy, non-treated controls." [b] Other Mental Health Diagnoses contains 1 study of patients whose primary diagnosis was PTSD, SUD, depression, anxiety, cognitive problems, or suicidal thoughts and behaviors.
Abbreviations. 5-MeO-DMT=5-methoxy-N,N-dimethyltryptamine, a psychedelic of the tryptamine class; CBCT=cognitive-behavioral conjoint therapy; CBT=cognitive behavioral therapy; DMT=5-methoxy-N,N-dimethyltryptamine; hr=hour; MDMA=3,4-methylenedioxy-methamphetamine; NR=not reported; OUD=opioid use disorder; pts=patients.

SETTING CHARACTERISTICS OF INCLUDED PRIMARY STUDIES

RCTs

Author Year	Treatment Setting	Treatment Administrators	Patient Instructions
Alcohol Use Disorder			
Bogenschutz 2022[1]	Living-room like setting, on a couch wearing eyeshades and headphones (providing a standardized program of music)	2 study therapists	NR
Major Depressive Disorder			
Carhart-Harris 2021[2]	Clinical	2 mental health professions; 1 of the pair was a clinical psychologist, psychotherapist, or psychiatrist, and the other could be an equivalent grade clinician or trainee	Visit 2: 1st treatment dose. Patients also instructed to take daily placebo capsules until next dose Visit 5: Psychological integration session, instruction to take placebo or escitalopram daily
Davis 2021[3] & Gukasyan 2022[4]	Living-room like setting, on a couch wearing eyeshades and headphones (providing a standardized program of music)	2 facilitators with varying educational levels (*ie*, bachelor's, master's, doctorate, and medical degrees) and professional disciplines (*eg*, social work, psychology, and psychiatry)	Focus their attention inward and stay with any experience that arose.
Palhano-Fontes 2019[5] & Zeifman 2019[6]	Quiet, comfortable living room-like environment	2 investigators remained in room next door offering help when needed	Asked to remain quiet with their eyes closed while focusing on their body, thoughts, and emotions.
Opioid Use Disorder			
Glue 2016[7]	NR	NR	Patients were given controlled release morphine and then immediate release morphine the week before ibogaine treatment. They were instructed to fast for 10 hours prior to ibogaine administration.

Author Year	Treatment Setting	Treatment Administrators	Patient Instructions
Posttraumatic Stress Disorder			
Bouso 2008[8] [a]	Clinical	2 therapists	After drug administration: Lay in bed with eyes closed, relaxation techniques Hours 1–2: Confront traumatic event Hours 3–6: Share experience, talk therapy Hours 6–8: Session conclusion, shared meal
Mitchell 2021[9]	NR	2-person therapy team; therapists had a master's degree or higher	Therapists helped participants work through memories of traumatic events, arrive at emotional resolution, and find new perspectives.
Mithoefer 2011[10] & Mithoefer 2013[11]	Comfortable, aesthetically pleasing outpatient office, patients reclining, listening to relaxing and then emotional evocative music	Male and female co-therapy team, 1 a psychiatrist and the other a psychiatric nurse	Equal balance between quiet introspection and therapeutic conversation
Mithoefer 2018[12]	NR	Male and female co-therapy team	NR
Mithoefer 2019[13] [b]	Designated are with futon or sofa with artwork or other objects to make the space esthetically pleasing	Male and female co-therapy team	Option to wear eye shades and listen to instrumental music and focus inward
Oehen 2013[14]	Group psychotherapy room at the primary investigator's clinic	1 male and 1 female therapist	NR
Ot'alora 2018[15]	Outpatient clinic furnished to look like a comfortable living room	Male and female co-therapy team	NR
NCT01958593	NR	Male and female co-therapy team	NR
NCT01689740	NR	Male and female co-therapy team	NR

Author Year	Treatment Setting	Treatment Administrators	Patient Instructions
Social Anxiety Disorder			
Dos Santos 2021[16]	NR	NR	Researchers used a nondirective, supportive approach during drug sessions. Participants instructed to "remain as quiet and introspective as possible, with your eyes open or closed, while focusing on your body, thoughts, and emotions."

Notes. [a] Bouso 2008 study terminated early due to "political pressure." [b] Mithoefer 2019 is a pooled analysis of Mithoefer 2011, Mithoefer 2018, Oehen 2013, Otalora 2018, NCT0195893, and NCT01689740.
Abbreviations. MRI=magnetic resonance imaging; NR=not reported.

Observational Studies

Author Year	Treatment Setting	Treatment Administrators	Patient Instructions
Alcohol Use Disorder			
Bogenschutz 2015[17]	Living-room like setting, on a couch wearing eyeshades and headphones (providing a standardized program of music)	2 study therapists	Direct attention toward their internal experience
Sessa 2021[18]	NR	2 clinicians trained in delivering MDMA-assisted psychotherapy	NR
Major Depressive Disorder			
Carhart-Harris 2016[19] & 2018[20]	Pre-decorated dosing room with low lighting	2 psychiatrists	Patients were invited to relax on a ward bed while music played through speakers/earphones.
Lyons 2018[21] [a]	Same as Carhart-Harris 2016	Same as Carhart-Harris 2016	Same as Carhart-Harris 2016
Osorio 2015[22]	Inpatient psychiatric ward, during treatment patients were seated in a comfortable recliner in a dimly lit room	NR	NR

Author Year	Treatment Setting	Treatment Administrators	Patient Instructions
Sanches 2016[23] & Zeifman 2021[24]	Quiet, dimly lit room	NR	NR
Stroud 2018[25] [a]	Pre-decorated room with low light, fabric drapes, flowers at side of bed	2 psychiatrists	NR
Obsessive Compulsive Disorder			
Moreno 2006[26]	Comfortable outpatient clinic setting	Principal investigator and trained sitter	Wear eye shades and listen to pre-determined music
Opioid Use Disorder			
Brown 2018[27]	NR	NR	Subjects were stabilized on short-acting opioids for 2–3 days prior to treatment. Test dose was administered in morning when subjects began feeling withdrawal symptoms.
Davis 2017[28]	Residential care facility for adults with SUD and MH problems	Clinical	None
Knuijver 2022[29]	Inpatient clinic	Clinical	None
Malcolm 2018[30]	Medically supervised inpatient setting	Clinical	Prior to treatment, patients were converted to short-acting opioids. They received a medical eval upon arrival at the clinic. Ibogaine was administered 4 hours after last morphine dose.
Noller 2018[31]	NR	2 ibogaine providers offering treatment on a fee-for-service basis, each associated with a physician. 1 was a registered addictions counselor.	NR
Posttraumatic Stress Disorder			
Jardim 2021[32]	NR	Clinical	NR
Monson 2020[33]	Combination of in person and video CBT sessions (MDMA sessions were in person)	Expert therapists in MDMA and CBCT	NR
Wang 2021[34]	NR	Clinical	Introspection of trauma-related memories and feelings

Author Year	Treatment Setting	Treatment Administrators	Patient Instructions
Substance Use Disorder			
Thomas 2013[35]	3-day spiritual retreat according to customs of Peruvian Shipibo people, during Ayahuasca sessions participants laid quietly on beds	Master Ayahuasquero	NR
Mash 2000[36]	Opiate detoxification facility	Clinical	NR
Mash 2001[37]	Opiate detoxification facility	Clinical	NR
Mash 2018[38]	Opiate detoxification facility	Clinical	NR
Schenberg 2014[39]	Private hospital room	Physician administering Tx stayed onsite the entire time, checking in on pt. every ~30 min	Encouraged patients to be quiet, calm, and confident. Patients were advised to stay away from others or social activity for 7 days after treatment.
Tobacco Addiction			
Johnson 2014[40] & 2017[41]	NR	Clinical	NR
Other Mental Health Diagnoses[b]			
Davis 2020[42]	Clinical/residential	Clinical	Patients were in a group setting, instructed to lie on a bed in a supine position. Integration session - Independent work, group discussion, psychological support

Notes. [a] Lyons 2018 and Stroud 2018 included comparison groups to "healthy, non-treated controls." [b] Other Mental Health Diagnoses contains 1 study of patients whose primary diagnosis was PTSD, SUD, depression, anxiety, cognitive problems, or suicidal thoughts and behaviors.
Abbreviations. 5-MeO-DMT=5-methoxy-N,N-dimethyltryptamine; CBCT=cognitive-behavioral conjoint therapy; CBT=cognitive behavioral therapy; MDMA=3,4-methylenedioxy-methamphetamine; MH=mental health; MRI=magnetic resonance imaging; NR=not reported; pt.=patient; SUD=substance use disorder.

OUTCOME DATA OF INCLUDED PRIMARY STUDIES

Disorder-specific Outcomes

Author Year ***N***	Study Design	Intervention ***Comparator***	Disorder-specific Outcomes
Alcohol Use Disorder			
Bogenschutz 2015[17] *N=10*	Pre-post	Psilocybin *None*	% heavy drinking days weeks 5–12 relative to baseline: [mean difference (SD) = 26.0 (22.4), 95% CI 8.7–43.2, p = 0.008] and relative weeks 1–4: [mean difference (SD) = 18.2 (20.0), 95% CI 2.8–33.5, *p* = 0.026] % drinking days weeks 5–12 relative to baseline: [mean difference (SD) = 27.2 (23.7), 95% CI 9.0–45.4, p = 0.009] and relative weeks 1–4: [mean difference (SD) = 21.9 (21.8), 95% CI 5.1–38.6, *p* = 0.017]
Bogenschutz 2022[1] *N=95*	RCT	Psilocybin *Diphenhydramine*	Mean (SD) % heavy drinking days at baseline and 32 weeks: 56.48 (31.77) and 9.71 (26.21) in the psilocybin group compared to 48.57 (28.73) and 23.57 (26.67) in the diphenhydramine group; between-group mean difference: 13.86 (95% CI 3.00, 24.72), *p* = .01 Mean (SD) % drinking days at baseline and 32 weeks: 78.03 (27.02) and 29.39 (32.86) in the psilocybin group compared to 71.68 (28.98) and 42.83 (33.43) in the diphenhydramine group; between-group mean difference: 13.44 (95% CI –0.18, 27.05), *p* = .05 Mean (SD) drinks per day at baseline and 32 weeks: 5.2 (2.81) and 1.17 (1.99) in the psilocybin group compared to 4.38 (2.39) and 2.26 (2.02) in the diphenhydramine group; between-group mean difference: 1.09 (95% CI 0.27, 1.92), *p* = .01
Sessa 2021[43] *N=14*	Pre-post	MDMA *None*	9 participants were abstinent from alcohol and 2 reduced use to <14 units of alcohol per week at 9 months follow-up

Author Year ***N***	**Study Design**	**Intervention** ***Comparator***	**Disorder-specific Outcomes**
Major Depressive Disorder			
Carhart-Harris 2016[19] & 2018[20] *N=20*	Pre-post	Psilocybin-assisted psychotherapy *None*	Mean change in QIDS-SR-16 from baseline to 6 months: − 14.9 (12.0), Cohen's *d* 1.4, *p* < 0.001 Mean reduction in suicidality scores on QIDS-SR-16 from baseline to 5 weeks: − 0.7, 95% CI = − 0.22 to − 1.2, *p* = 0.01 Relapse rate (QIDS score of 6+ or above) at 6 months among responders: 3/9 (33%)
Carhart-Harris 2021[2] *N=59*	RCT	Psilocybin-assisted psychotherapy *Low-dose psilocybin & escitalopram*	Mean (±SE) change in QIDS-SR-16 from baseline to week 6: −8.0±1.0 in the psilocybin group and −6.0±1.0 in the escitalopram group (difference, −2.0; 95% CI, −5.0 to 0.9; *p* = 0.17)
Davis 2021[3] & Gukasyan 2022[4] *N=27*	RCT	Psilocybin-assisted psychotherapy *Delayed treatment*	Mean (±1 SD) GRID-HAMD at baseline 22.9 (3.6) and at 8 weeks 8.5 (5.7) for the immediate treatment group and 22.5 (4.4) at baseline and 23.5 (6.0) at 8 weeks for the delayed treatment group, Cohen's *d* = 2.6; 95% CI, 1.5-3.7; *p* < .001 For all participants: Mean (±1 SD) GRID-HAMD at baseline 22.8 (3.9) and at 12 months 7.7 (7.9); Cohen's *d* (95% CI) 2.4 (1.6–3.2) at 12 months
Lyons 2018[21] [a] *N=30*	Open-label mixed design	Psilocybin-assisted psychotherapy *Healthy untreated patients*	Mean BDI at baseline (M = 34.33, SD = 7.44) and 1 week after psilocybin sessions (M = 12.13, SD = 9.80); t(14) = 7.900, 95% CI (16.17, 28.23) *p* < 0.001 No significant difference found in baseline vs follow-up BDI scores among the healthy comparison group.
Osorio 2015[22] *N=6*	Pre-post	Ayahuasca *None*	Reduction in mean HAM-D by 62% on day 1 (*p* = 0.01), 72% on day 7 (*p* = 0.001), and 45% on day 14 (*p* = 0.11). Scores significantly decreased at day 21 but % NR.
Palhano-Fontes 2019[5] *N=29*	RCT	Ayahuasca *0mg placebo*	Mean (SD) HAM-D at baseline and 1 week after dosing in the ayahuasca group: 24.07 (5.34) and 9.72 (7.39) compared to the placebo group: 19.73 (4.59) and 16.92 (7.36), within group Cohen's *d* = 2.22 (95% CI 1.28, 3.17) in the ayahuasca group compared to Cohen's *d* = 0.46 (95% CI -0.27, 1.18)

Author Year ***N***	**Study Design**	**Intervention** ***Comparator***	**Disorder-specific Outcomes**
Sanches 2016[23] & Zeifman 2021[24] *N=17*	Pre-post	Ayahuasca *None*	Administration of ayahuasca was associated with significant HAM-D and MADRS score decreases from 80 to 180 minutes ($p < 0.01$) and day 1 to day 21 ($p = 0.000$). Acute changes in suicidality (N=15): significant effect for time ($F(4,13.85) = 7.17$; $p = 0.002$). Within-subject t tests found the largest effect size at 180 min after administration (Hedges' $g = 0.89$). Post-acute changes in suicidality (N=15): significant effect for time($F(4,10.69) = 15.65$; $p < 0.001$). Within-subject t tests found significant decreases in suicidality between baseline and 1, 7, 14, and 21 days after administration with the largest effect at 21 days (g = 1.75).
Stroud 2018[25] [a] *N=32*	Pre-post	Psilocybin-assisted psychotherapy *Healthy untreated patients*	Mean QIDS-16 at baseline (M = 18.88, SD = 2.23) and 1 week after psilocybin sessions (M= 7.65, SD = 5.34) ($p < .001$) No significant difference found in baseline vs follow-up QIDS-16 scores among the healthy comparison group.
Opioid Use			
Brown 2018[27] *N=30*	Pre-post	Ibogaine *None*	Mean reduction in SOWS at mean time interval between first and second SOWS 76.5 ± 30 hrs: 17.0 ± 12.5 points ($t = 7.07$, $df = 26$, $p < .001$) ASI for drug use at baseline: 0.40 ± 0.08; at 12 months: 0.17 ± 0.10 Participants with opioid-free days in the previous 30 days at 12 months (missing values set to pretreatment baseline): 8.8 ± 12.7
Davis 2017[28] *N=88*	Pre-post	Ibogaine and participation in detoxification program *None*	% participants with reduction in cravings: 50% at 1 week; 35% at 3 or more months Opioid use post-treatment: 30% abstinent (variable duration); 48% returned to use; 17% no change; 6% use increased
Glue 2016[7] *N=27*	RCT	Noribogaine *0mg placebo*	Mean time to opioid substitution treatment: 8.6 hours in 60mg group, 22.5 hours in 120mg group, and 11.4 hours in 180mg group, and 13.9 hours in placebo group

Author Year ***N***	**Study Design**	**Intervention** ***Comparator***	**Disorder-specific Outcomes**
Knuijver 2022[29]	Pre-post	Ibogaine	Return to morphine use within 24 hours: 11/14 (79%); Median COWS among 5 not on morphine after 24 hours: 0
N=14		*None*	
Malcolm 2018[30]	Pre-post	Ibogaine and participation in detoxification program	Pre-ibogaine mean COWS: 8.2 ± 5.21 at 48 hours and 7.64 ± 5.27 at 24 hours; post-ibogaine mean COWS: 5.26 ± 4.31 at 24 hours and 3.30 ± 3.13) at 48 hours
N=50			Pre-ibogaine mean SOWS: 20.51 ± 13.66 at 48 hours and 17.09 ± 12.95 at 24 hours; post-ibogaine mean SOWS: 12.63 ± 11.95 at 24 hours and 10.04 ± 11.65 at 48 hours
			Pre-ibogaine mean BSCS: 6.58 ± 3.08 at 48 hours and 5.98 ± 2.98 at 24 hours; post-ibogaine mean BSCS: 2.69 ± 2.68 at 24 hours and 1.92 ± 2.83 at 48 hours
Noller 2018[31]	Pre-post	Ibogaine and concomitant	Mean SOWS (N=14) at baseline 25.21 (SD 12.57) and 12-24 hours 14.21 (SD 14.08), $p = 0.015$
N=14		*Diazepam and zopiclone*	Mean SOWS (N=6) at baseline 24 (SD 16.84) and 42-84 hours 8.5 (SD 3.72), $p = 0.070$
			ASI for drug use (N=8) 0.32 (SD 0.07) at baseline compared to 0.06 (SD 0.08) $p < 0.01$ at 12-month follow-up
			Negative urine drug screen at 12 months (N=8): 6/8, 75%
Posttraumatic Stress Disorder			
Bouso 2008[8]	RCT	MDMA-assisted psychotherapy	Mean SSSPTSD at baseline and post-treatment for the 50mg group: 37.3 vs 28.3 compared to the placebo group: 44.5 vs 40
N=6		*0mg placebo*	Mean SSSPTSD at baseline and post-treatment for 1 participant who received 75mg: 48 vs 32

Author Year ***N***	**Study Design**	**Intervention** ***Comparator***	**Disorder-specific Outcomes**
Jardim 2021[32] *N=3*	Pre-post	MDMA-assisted psychotherapy *None*	CAPS-5 at baseline per participant: 90, 78, and 72; 2 months post-treatment: 61, 27, and 8 respectively PCL-C at baseline per participant: 69, 59, 55; 2 months post-treatment: 57, 49, 20 respectively PTGI at baseline per participant: 9, 34, and 11; 2 months post-treatment: 66, 86, and 60 respectively
Mitchell 2021[9 a] *N=90*	RCT	MDMA-assisted psychotherapy *0mg placebo*	Participants no longer meeting PTSD diagnostic criteria: 14/42 (33%) MDMA group vs 2/37 (5%) placebo group
Mithoefer 2011[10 b] & Mithoefer 2013[11] *N=20*	RCT	MDMA-assisted psychotherapy *0mg placebo*	Participants no longer meeting PTSD diagnostic criteria: 10/12 (83%) in MDMA group vs 2/8 (25%) in placebo group Participants with >30% reduction from baseline in CAPS total severity score: 10/12 (83%) in MDMA group vs 2/8 (25%) in placebo group
Mithoefer 2018[12 b] *N=26*	RCT	MDMA-assisted psychotherapy *Active control*	Participants no longer meeting PTSD diagnostic criteria at 1 month follow-up: 6/7 (86%) of 75mg group, 7/12 (58%) of 125mg group, and 2/7 (29%) of control group Participants with >30% decrease in CAPS-4 total score at 1 month follow-up: 7/7 (100%) of 75mg group, 8/12 (67%) of 125mg group, and 2/7 (29%) of control group
Mithoefer 2019[13] *N=105*	RCT	MDMA-assisted psychotherapy *0mg placebo or active control*	Pooled data from 6 RCTs: the active MDMA group had significantly greater reductions in CAPS-IV total scores from baseline than the control group [MMRM estimated mean difference (SE) between groups - 22.0 (5.17), $p < 0.001$].
Monson 2020[33] *N=12*	Pre-post	MDMA and cognitive-behavioral conjoint therapy *None*	Mean (SD) CAPS-5 at baseline: 41.42 (5.76) and at 6 months: 15.52 (15.22) Patient PTSD Checklist-5: 62.64 (6.35) at baseline and 17.20 (16.76) at 6 months Partner-rated PTSD Checklist at baseline: 49.58 (8.52) at baseline and 16.64 (14.84) at 6 months

Author Year ***N***	**Study Design**	**Intervention** ***Comparator***	**Disorder-specific Outcomes**
Oehen 2013[14 b] *N=12*	RCT	MDMA-assisted psychotherapy *Active control*	Participants with >30% decrease in CAPS-4 total score at 12-month follow-up after all had received full-dose MDMA: 9/12 (75%)
Ot'alora 2018[15 b] *N=28*	RCT	MDMA-assisted psychotherapy *Active control*	Participants no longer meeting PTSD diagnostic criteria at 12-month follow-up: 4/9 (44%) of 100mg group, 5/12 (42%) of 125mg group, and 2/6 (33%) of control group Participants with >30% decrease in CAPS-4 total score at 12-month follow-up: 5/9 (56%) of 100mg group, 6/12 (50%) of 125mg group, and 1/6 (17%) of control group
NCT01689740[44 b] *N=8*	RCT	MDMA-assisted psychotherapy *Active control*	See pooled analysis table
NCT01958593[45 b] *N=6*	RCT	MDMA-assisted psychotherapy *0mg placebo*	See pooled analysis table
Wang 2021[34] *N=37*	Pre-post	MDMA-assisted psychotherapy	Mean (SD) change CAPS-5: −29.89 (13.45)
Substance Use Disorder			
Thomas 2013[35] *N=12*	Pre-post	Ayahuasca *None*	No change was observed for opiate or cannabis use, and no serious adverse events were reported.
Mash 2000[36] *N=27*	Pre-post	Ibogaine and participation in detoxification program *None*	Ibogaine significantly decreased craving for cocaine and heroin during inpatient detoxification.

Author Year ***N***	**Study Design**	**Intervention** ***Comparator***	**Disorder-specific Outcomes**
Mash 2001[37] *N=32*	Pre-post	Ibogaine and participation in detoxification program *None*	Mean OOWS: 5.75 at 12 hours from last opiate dose (pre-ibogaine); mean OOWS 1.25 at 24 hours and 2 at 36 hours from last opiate dose (post-ibogaine)* Pre-ibogaine mean OP-SCL: 22 at 24 hours; post-ibogaine OP-SCL: 13 within 72 hours and 7 at 6-9 days*
Mash 2018[38] N=191	Pre-post	Ibogaine and participation in detoxification program *None*	Self-reported cravings as measured by the Heroin (HCQ-29) and Cocaine (CCQ-45) Craving Questionnaires were lower at the time of discharge compared to before treatment and remained lower among 37 participants with opioid dependence and 32 with cocaine dependence who completed follow-up at 1 month.
Schenberg 2014[39] *N=75*	Pre-post	Ibogaine *None*	The duration of reported abstinence was longer for participants who underwent multiple ibogaine dosing sessions compared to 1 dosing session (median 8.4 months compared to median 5.5 months).
Tobacco Addiction			
Johnson 2014[40] & 2017[41] *N=15*	Pre-post	Psilocybin *None*	10/15 (67%) participants showed 7-day point prevalence abstinence as measured by smoking timeline follow-back assessments and verified by exhaled carbon monoxide and urinary cotinine levels. 9/12 (60%) smoking abstinent at mean 30 months post-TQD; range = 16–57 months
Other Mental Health Diagnoses[b]			
Davis 2020[42] *N=51*	Pre-post	Ibogaine *None*	Significant reductions in PTSD symptoms (SMD PTSD Checklist-5 = –3.6, $p < 0.001$), depression (SMD Patient Health Questionnaire-2 = -3.7, $p < 0.001$), anxiety (SMD Generalized Anxiety Disorder 2-Item = -3.1, $p < 0.001$), and suicidal ideation (SMD Depressive Symptom Index Suicidality Subscale = -1.9, $p < 0.001$) 30-days post-treatment
Social Anxiety Disorder			
Dos Santos 2021[16] *N=17*	RCT	Ayahuasca *Placebo*	Compared with placebo, ayahuasca was associated with significant increases in self-perception during the public speaking test (F1,12 = 7.740, $p = 0.017$, .2 = 0.392).

Notes. [a] Intervention group also formed part of the sample in Carhart-Harris 2016 and Carhart-Harris 2018. [b] Mean change scores abstracted for pooled analysis. *Abbreviations.* ASI=Addiction Severity Index; BDI=Beck Depression Inventory; BSCS=Brief Substance Craving Scale; CAPS-4/5=Clinician Administered PTSD Scale for Diagnostic and Statistical Manual of Mental Disorders 4th/5th Edition; CI=confidence interval; COWS=Clinical Opioid Withdrawal Scale; GRID-HAM-

D=GRID-Hamilton Depression Rating Scale; HAM-D=Hamilton Depression Rating Scale; MADRS=Montgomery-Asberg Depression Rating Scale; MDMA=3,4-methylenedioxy-methamphetamine; NR=not reported; OOWS=Objective Opiate Withdrawal Scale; OP-SCL=Opiate Symptom Checklist; PCL-C=PTSD Checklist Civilian Version; PTGI=Posttraumatic Growth Inventory; PTSD=posttraumatic stress disorder; QIDS-SR-16=16-item Quick Inventory of Depressive Symptomatology; RCT=randomized controlled trial; SD=standard deviation; SE=standard error; SOWS=Subjective Opioid Withdrawal Scale; SSSPTSD=Severity of Symptoms Scale for Posttraumatic Stress Disorder.

Studies Used in Pooled Analysis (MDMA for PTSD)

Author Year	Comparator	MDMA Dose	N Overall	N MDMA	N Comparator	Outcome Timing	MDMA Mean (SD)	Comparator Mean (SD)
Mitchell 2021[9]	Placebo (0mg)	80-120 mg + supplemental dose of 40–60mg	N=79	N=42	N=37	18 weeks after baseline (T4)	-24.4 (11.6)	-13.9 (11.5)
Mithoefer 2011[10]	Placebo (0mg)	125mg + supplemental dose of 62.5mg	N=20	N=12	N=8	2 months after 2nd MDMA session (T4)	-55.2 (33.54)	-20.5 (20.47)
Mithoefer 2018[12]	Active control (30mg)	125mg	N=19	N=12	N=7	1 month after 2nd MDMA session	-44.3 (28.7)	-11.4 (12.7)
NCT01958593[4,5]	Placebo (0mg)	NR	N=6	N=4	N=2	1 month after 2nd MDMA session	-17.3 (13.05)	-21.5 (12.02)
NCT01689740[4,4]	Active control (25mg + 12.5mg)	125mg + 62.5mg supplemental dose	N=8	N=5	N=3	1 month after 2nd MDMA session	-34.6 (16.29)	-9 (15.62)
Oehen 2013[14]	Active control (25mg + 12.5mg)	125mg + 62.5mg supplemental dose	N=12	N=8	N=4	3 weeks after 3rd MDMA session (T2)	-15.6 (18.1)	3.1 (15.3)
Ot'alora 2018[15]	Active control (40mg)	125mg	N=18	N=12	N=6	1 month after 2nd MDMA session	-29.2 (29.62)	-11.5 (21.21)

Abbreviations. MDMA=3,4-methylenedioxy-methamphetamine; NR=not reported; SD=standard deviation; T2/4=Timepoint 2/4.

Harms

Ayahuasca

Author, Year Diagnosis N	Headache	Nausea	Diarrhea	Vomiting	Anxiety	Restless-ness	Drowsiness	Confu-sion	Fear	Distress	Dissocia-tion/ Deperson-alization
Dos Santos, 2021[16] Social Anxiety Disorder N=17	2 (11.8%)	4 (23.5%)[a]	1 (5.9%)	3 (17.6%)	—	—	2 (11.8%)	2 (11.8%)	1 (5.9%)	1 (5.9%)	1 (5.9%)
Osorio, 2015[22] MDD N=6	—	—	—	3 (50%)	—	—	—	—	—	—	—
Palhano-Fontes, 2019[5] MDD N=29 (14 vs 15) [b]	6 (42%) vs 8 (53%)	10 (71%) vs 4 (26%)	—	8 (57%) vs 0 (0%)	7 (50%) vs 11 (73%)	7 (50%) vs 3 (20%)	—	—	—	—	—

Author, Year Diagnosis N	Headache	Nausea	Diarrhea	Vomiting	Anxiety	Restless-ness	Drowsiness	Confu-sion	Fear	Distress	Dissocia-tion/ Deperson-alization
Sanches, 2016[23] MDD N=17	—	—	—	8 (47%)	—	—	—	—	—	—	—
Zeifman, 2021[24] MDD N=17	—	—	—	—	—	—	—	—	—	—	—

Notes. [a] Item is reported as "gastrointestinal discomfort and nausea." [b] Data are reported as "treatment group vs control group," respectively.
Abbreviations. MDD=major depressive disorder.

Ibogaine

Author, Year Diagnosis N	Headache	Nausea	Vomiting	QTc > 500ms Event	Bradycardia	Death	Visual Impairment
Glue, 2016[7] OUD 27 (60mg: 6 120mg: 6	60mg: 4 (66.7%) 120mg: 2 (33.3%) 180mg: 2 (33.3%) Placebo: 5 (55.6%)	60mg: 0 120mg: 2 (33.3%) 180mg: 2 (33.3%) Placebo: 1 (11.1%)	—	—	—	—	60mg: 2 (33.3%) 120mg: 5 (83.3%) 180mg: 4 (66.7%) Placebo: 2 (22.2%)

Author, Year Diagnosis N	Headache	Nausea	Vomiting	QTc > 500ms Event	Bradycardia	Death	Visual Impairment
180mg: 6 Placebo: 9)							
Knuijver, 2022[29] OUD N=14	—	—	2 (14.3%)	7 (50%)	7 (50%)	—	—
Noller, 2018[31] OUD N=14	—	—	—	—	—	1 (7.1%)	—

Abbreviations. OUD=opioid use disorder.

MDMA

Note: An analytic dataset of effect sizes used in reported meta-analyses is available upon request to esp.cc@va.gov.

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
During Session								
Jardim, 2021[32 a]	Irritability: 1 Anguish: 2	Insomnia: 1 Fatigue: 1	Dizziness: 1	—	Cough: 3	—	Pain: 1	Somatic pains: 4

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
PTSD N=3	Colic: 2 Despair: 1 Rage: 1 Sadness: 1				Nasal congestion: 1			
Mithoefer, 2011[10] PTSD N=20 (12 vs 8)	Anxiety: 14 (58%) vs 13 (81%) Restlessness: 5 (21%) vs 2 (13%) Low mood: 4 (17%) vs 2 (13%) Irritability: 2 (8%) vs 3 (19%) Rumination/ increased private worries: 1 (4%) vs 1 (6%) Difficulty concentrating: 3 (13%) vs 1 (6%)	Insomnia: 13 (54%) vs 10 (63%) Drowsiness: 2 (8%) vs 3 (19%) Need more sleep: 0 vs 1 (6%) Fatigue: 11 (46%) vs 8 (50%) Weakness: 1 (4%) vs 1 (6%)	Dizziness: 9 (38%) vs 2 (13%) Impaired balance/gait: 6 (25%) vs 0 Visual impairment/ disturbance: 1 (4%) vs 0 Nystagmus: 1 (4%) vs 0 Paresthesia/ tingling Sensation: 2 (8%) vs 0	—	—	Nausea: 12 (50%) vs 2 (13%) Upper GI burning: 1 (4%) vs 0 Reduced/ lack of appetite: 8 (33%) vs 1 (6%)	Headache: 14 (58%) vs 9 (56%) Pain: 1 (4%) vs 4 (25%) Jaw clenching/ tight jaw: 19 (79%) vs 3 (19%) Muscle tension: 4 (17%) vs 2 (13%)	Heavy legs: 2 (8%) vs 0 Somatic sensations: 1 (4%) vs 0 Sensitivity to cold/feeling cold: 10 (42%) vs 8 (50%) Dry mouth: 4 (17%) vs 1 (6%) Thirst: 2 (8%) vs 1 (6%)

Author, Year **Diagnosis** **N** **Follow-up**	**Psychiatric**	**Sleep/ Fatigue**	**Neurologic/ Sensory**	**Cardiac**	**ENT/ Respiratory**	**GI**	**Musculo-skeletal**	**Other**
								Perspiration: 4 (17%) vs 1 (6%) General infection: 1 (4%) vs 0
Mithoefer, 2018[12] PTSD N=26 30mg: 7 75mg: 7 125mg: 12	Anxiety: 4 (57%) vs 6 (86%) vs 11 (92%) Restlessness: 4 (57%) vs 5 (71%) vs 3 (25%) Suicidal ideation: 1 (3.8%) Depression: 1 (3.8%)	Fatigue: 5 (71%) vs 4 (57%) vs 7 (58%)	—	Premature ventricular contraction: 1 (3.8%)	—	Reduced/ lack of Appetite: 3 (43%) vs 4 (57%) vs 8 (67%) Appendicitis: 1 (3.8%)	Headache: 5 (71%) vs 5 (71%) vs 8 (67%) Jaw clenching/ tight jaw: 0 vs 4 (57%) vs 9 (75%) Muscle tension: 4 (57%) vs 3 (43%) vs 9 (75%)	Sensitivity to cold/feeling cold: 4 (57%) vs 4 (57%) vs 6 (50%) Perspiration: 2 (29%) vs 2 (29%) vs 5 (42%)
Monson, 2020[33] PTSD N=12	Anxiety: 1 (16.7%) vs 1 (16.7%) Difficulty con-centrating: 1 (16.7%) vs 1 (16.7%)	Insomnia: 0 vs 1 (16.7%) Fatigue: 2 (33.3%) vs 0	Tremor: 1 (16.7%) vs 0 Tic: 1 (16.7%) vs 0	—	Upper respiratory infection: 2 (33.3%) vs 1 (16.7%)	Nausea: 2 (33.3%) vs 0 Vomiting: 0 vs 1 (16.7%)	Oropharyn-geal pain: 0 vs 1 (16.7%) Painful urination: 1 (16.7%) vs 0	Skin irritation [b]: 1 (16.7%) vs 2 (33.3%)[b] Arthoropod bite: 0 vs 1 (16.7%)

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
		Weakness: 1 (16.7%) vs 0	Dizziness: 0 vs 1 (16.7%) Visual impairment/ disturbance: 0 vs 1 (16.7%) Paresthesia/ tingling sensation: 0 vs 1 (16.7%)		Sinusitis: 1 (16.7%) vs 0 Nasopharyn-gitis: 1 (16.7%) vs 0 Runny nose: 0 vs 1 (16.7%) Nasal congestion: 0 vs 1 (16.7%) Shortness of breath: 0 vs 1 (16.7%) Tinnitus: 1 (16.7%) vs 0	Reduced/ lack of appetite: 2 (33.3%) vs 0		
Oehen, 2013[14] [c] PTSD N=12 (8 vs 4)	Anxiety: 10 (25%) / 1 (16%) vs 2 (15%) Restlessness: 15 (41%) / 2 (33%) vs NA Low mood: 4 (11%) / 0 vs 1 (8%)	Insomnia: 16 (43%) / 2 (50%) vs 4 (31%) Drowsiness: 2 (5%) / 0 vs 0	Dizziness: 8 (22%) / 3 (60%) vs 4 (31%) Impaired balance/gait: 12 (32%) / 4	—	—	Nausea: 6 (16%) / 2 (33%) vs 2 (15%) Reduced/ lack of appetite: 15	Headache: 11 (30%) / 2 (33%) vs 5 (38%) Jaw clenching/ tight jaw: 14	Heavy legs: 1 (3%) / 1 (16%) vs 0 Sensitivity to cold/feeling cold: 11 (30%) / 0 vs 1 (8%)

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
	Rumination/ Increased private worries: 2 (5%) / 0 vs 0 Difficulty concentrating: 6 (16%) / 0 vs 0	Need more sleep: 1 (3%) / 0 vs 0 Fatigue: 12 (35%) / 1 (16%) vs 2 (15%) Weakness: 3 (8%) / 1 (16%) vs 0	(66%) vs 3 (23%) Nystagmus: 3 (8%) / 1 (16%) vs 0 Paresthesia/ tingling sensation: 2 (5%) / 1 (16%) vs 0			(41%) / 2 (33%) vs 4 (31%)	(38%) / 4 (66%) vs 1 (8%)	Dry mouth: 7 (19%) / 2 (33%) vs 0 Thirst: 13 (35%) / 2 (33%) vs 0 Perspiration: 6 (16%) / 2 (33%) vs 0
Ot'alora, 2018[15] PTSD N=28 40mg: 6 100mg: 9 125mg: 13	Anxiety: • 40mg: 2 (33.3%) • 100mg: 6 (66.7%) • 125mg:7 (53.8%) • Total: 17 (60.7%) Low mood: 40mg: 0 • 100mg: 5 (55.6%) • 125mg: 2 (15.4%) • Total: 7 (25%)	Fatigue: • 40mg: 2 (33.3%) • 100mg: 4 (44.4%) • 125mg: 4 (30.8%) • Total: 11 (39.3%)	Dizziness: • 40mg: 1 (16.7%) • 100mg: 2 (22.2%) • 125mg: 7 (53.8%) • Total: 12 (42.9%)	—	—	—	Headache: • 40mg: 4 (66.7%) • 100mg: 4 (44.4%) • 125mg: 3 (23.1%) • Total: 13 (46.4%) Jaw clenching/ tight jaw: • 40mg: 2 (33.3%)	

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
							• 100mg: 5 (55.6%) • 125mg: 8 (61.5%) • Total: 18 (64.3%) Muscle tension: • 40mg: 2 (33.3%) • 100mg: 4 (44.4%) • 125mg: 7 (53.8%) • Total: 13 (46.4%)	
Sessa, 2021[43] AUD N=14	—	—	—	Rise in blood pressure: 1 (7.1%)	—	—	—	—
Wang, 2021[34] PTSD	Anxiety: 7 (19%) Suicidal ideation: 1 (3%)	Insomnia: 18 (49%) Fatigue: 5 (14%)	Dizziness: 9 (24%) Nystagmus: 11 (30%)	Palpita-tions/ Tachycar-dia: 3 (8%)	—	Nausea: 10 (27%)	Headache: 23 (62%) Pain in jaw: 3 (8%)	Perspiration: 4 (11%)

Author, Year **Diagnosis** **N** **Follow-up**	**Psychiatric**	**Sleep/ Fatigue**	**Neurologic/ Sensory**	**Cardiac**	**ENT/ Respiratory**	**GI**	**Musculo-skeletal**	**Other**
N=37			Vision blurred: 2 (5%) Paresthesia/ Tingling sensation: 3 (8%)			Reduced/lack of appetite: 7 (19%) Abdominal discomfort: 2 (5%)	Muscle tension: 27 (73%)	
Post-session								
Mithoefer, 2018[12] PTSD N=26 30mg: 7 75mg: 7 125mg: 12 Follow-up: 7 days	Anxiety: • 30mg: 4 (57%) • 75mg: 5 (71%) • 125mg: 10 (83%) • Total: 19 (73%) Low mood: • 30mg: 3 (43%) • 75mg: 0 • 125mg: 3 (25%) • Total: 6 (23%) Irritability: • 30mg: 4 (57%) • 75mg: 2 (29%) • 125mg: 6 (50%) • Total: 12 (46%)	Insomnia: • 30mg: 5 (71%) • 75mg: 3 (43%) • 125mg: 10 (83%) • Total: 18 (69%) Fatigue: • 30mg: 6 (86%) • 75mg: 7 (100%) • 125mg: 10 (83%) • Total: 23 (88%)	—	—	—	Reduced/ lack of appetite: • 30mg: 2 (29%) • 75mg: 1 (14%) • 125mg: 6 (50%) • Total: 9 (35%)	Headache: • 30mg: 2 (29%) • 75mg: 3 (43%) • 125mg: 7 (57%) • Total: 12 (46%) Muscle tension: • 30mg: 2 (29%) • 75mg: 3 (43%) • 125mg: 7 (58%)	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
	Difficulty concentrating: • 30mg: 2 (29%) • 75mg: 0 • 125mg: 5 (42%) • Total: 7 (27%)	Need more sleep: • 30mg: 6 (86%) • 75mg: 6 (86%) • 125mg: 9 (75%) • Total: 21 (81%)					• Total: 12 (46%)	
Mithoefer, 2011[10] PTSD N=20 (12 vs 8) Follow-up: 7 days	Anxiety: 13 (54%) vs 7 (44%) Restlessness: 1 (4%) vs 0 Distress/panic/ stress: 1 (4%) vs 1 (6%) Dissociation/ depersonalize-ation/derealiz-ation/detachment: 1 (4%) vs 0 Low mood: 10 (42%) vs 8 (50%)	Insomnia: 9 (38%) vs 9 (56%) Drowsiness: 0 vs 2 (13%) Fatigue: 18 (75%) vs 12 (75%) Need more sleep: 5 (21%) vs 2 (13%) Weakness: 6 (25%) vs 0	Dizziness: 3 (13%) vs 1 (6%) Visual impairment/ Disturbance: 2 (8%) vs 0	—	Upper respiratory infection: 2 (8%) vs 2 (13%)	Nausea: 7 (29%) vs 4 (25%) Diarrhea: 3 (13%) vs 0 Reduced/ lack of appetite: 9 (38%) vs 0	Headache: 6 (25%) vs 4 (25%) Jaw clenching/ tight jaw: 6 (25%) vs 2 (13%) Muscle tension: 2 (8%) vs 1 (6%)	Perspiration: 0 vs 1 (6%) Sensitivity to cold/feeling cold: 18 (75%) vs 12 (75%) Dry mouth: 1 (4%) vs 0 General infection: 0 vs 2 (13%) Heavy legs: 1 (4%) vs 0

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
	Irritability: 8 (33%) vs 3 (19%) Difficulty concentrating: 6 (25%) vs 0 Rumination/ increased private worries: 3 (13%) vs 2 (13%)							Pain: 1 (4%) vs 1 (6%) Somatic sensations: 1 (4%) vs 0
Oehen, 2013[14 d] PTSD N=12 (8 vs 4) Follow up: 7	Anxiety: 11 (26%) vs 2 (15%) Restlessness: 6 (14%) vs 0 Distress/panic/ Stress: 1 Low mood: 20 (47%) vs 6 (46%) Irritability: 9 (21%) vs 1 (8%)	Insomnia: 20 (47%) vs 6 (46%) Drowsiness: 2 (5%) vs 1 (8%) Fatigue: 24 (56%) vs 5 (38%) Need more sleep: 6 (14%) vs 3 (23%)	Dizziness: 8 (18%) vs 3 (23%) Nystagmus: 1 (2%) vs 0 Impaired balance/gait: 3 (7%) vs 0	—	—	Nausea: 5 (12%) vs 2 (15%) Reduced/ lack of appetite: 7 (16%) vs 5 (38%)	Headache: 10 (23%) vs 4 (31%) Jaw clenching/ tight jaw: 7 (16%) vs 0	Perspiration: 1 (2%) vs 0 Sensitivity to cold/feeling cold: 6 (14%) vs 1 (8%) Dry mouth: 5 (12%) vs 0 Heavy legs: 0 vs 1 (8%) Thirst: 1 (2%) vs 0

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
	Difficulty concentrating: 10 (23%) vs 0 Rumination/ increased private worries: 9 (21%) vs 3 (23%)	Weakness: 5 (12%) vs 0						
Monson, 2020[33] PTSD N=12 Follow-up: 6 months	—	—	—	—	—	—	—	Urithritis/UTI: 1 (16.7%) vs 0 Hypothyroid-ism: 1 (16.7%) vs 0 Tooth infection: 1 (16.7%) vs 0 Abortion: 0 vs 1 (16.7%)
Ot'alora, 2018[15] PTSD N=28 40mg: 6	Anxiety: • 40mg: 2 (33.3%) • 100mg: 8 (88.9%) • 125mg: 10 (76.9%) • Total: 20 (71.4) Low mood:	Insomnia: • 40mg: 3 (50%) • 100mg: 7 (77.8%) • 125mg: 6 (46.2%)	—	—	—	Nausea: • 40mg: 1 (16.7%) • 100mg: 3 (33.3%) • 125mg: 8 (61.5%)	Headache: • 40mg: 4 (66.7%) • 100mg: 3 (33.3%) • 125mg: 5 (38.5%)	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
100mg: 9 125mg: 13 Follow-up: 7 days	• 40mg: 2 (33.3%) • 100mg: 6 (66.7%) • 125mg: 9 (69.2%) • Total: 17 (60.7%) Irritability: • 40mg: 2 (33.3%) • 100mg: 5 (55.6%) • 125mg: 6 (46.2%) • Total: 13 (46.4%) Difficulty concentrating: • 40mg: 2 (33.3%) • 100mg: 5 (55.6%) • 125mg: 2 (15.4%) • Total: 9 (32.1%) Rumination/ increased private worries: • 40mg: 1 (16.7%) • 100mg: 5 (55.6%) • 125mg: 6 (46.2%) • Total: 12 (42.9%)	• Total: 16 (57.1%) Fatigue: • 40mg: 2 (33.3%) • 100mg: 7 (77.8%) • 125mg: 9 (69.2%) • Total: 18 (64.3%) Need more sleep: • 40mg: 2 (33.3%) • 100mg: 5 (55.6%) • 125mg: 8 (61.5%) • Total: 15 (53.6%)				• Total: 12 (42.9%) Reduced/ lack of appetite: • 40mg: 1 (16.7%) • 100mg: 1 (11.1%) • 125mg: 8 (61.5%) • Total: 10 (35.7%)	• Total: 12 (42.9%) Muscle tension: • 40mg: 2 (33.3%) • 100mg: 1 (11.1%) • 125mg: 6 (46.2%) • Total: 9 (32.1%)	

Author, Year **Diagnosis** **N** **Follow-up**	**Psychiatric**	**Sleep/ Fatigue**	**Neurologic/ Sensory**	**Cardiac**	**ENT/ Respiratory**	**GI**	**Musculo-skeletal**	**Other**
Jardim, 2021[32] PTSD N=3 Follow-up: 7 days	Fear: 1 Anguish: 10	Fatigue: 3 Nightmares: 1 Sleepless-ness: 1	—	—	Cough: 2	—	Headache: 3 Muscle tension: 1	Pain: 1 Somatic pains: 3
Bouso, 2008[8] PTSD N=6 Follow-up: 24 hours	Depression: 1 Difficulty concentrating: 1 Failing memory: 1 Tension/inner unrest: 2 Emotional indifference: 1	Sleepiness: 2 Fatigue: 2	Visual impairment/ Disturbance: 1	Palpita-tions/ tachycard-ia: 1	—	Diarrhea: 1	Tension headache/ migraine: 2	Lack of libido: 1
Wang, 2021[34] PTSD N=37	Anxiety: • 1 day: 1 (3%) • 2 days: 2 (5%) Suicidal ideation: • 1 Day: 2 (5%)	Insomnia: • 1 day: 2 (5%) • 2 days: 3 (8%) Fatigue:	Dizziness: • 1 day: 3 (8%) • 2 days: 0	Palpita-tions/ Tachycard-ia: • 1 day: 1 (3%) • 2 days: 0	—	Nausea: • 1 day: 3 (8) • 2 days: 0 Reduced/lac k of appetite:	Headache: • 1 day: 13 (35%) • 2 days: 1 (3%)	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
Follow-up: 1-2 days	• 2 days: 1 (3%)	• 1 day: 3 (8%) • 2 days: 2 (5%)				• 1 day: 1 (3%) • 2 days: 0 Abdominal discomfort: • 1 day: 1 (3%) • 2 days: 0	Jaw clenching/ tight jaw: • 1 day: 1 (3%) • 2 days: 1 (3%)	
Total/Timing Unspecified								
Sessa, 2021[43] AUD N=14				Rise in blood pressure: 1				
Mithoefer, 2018[12] PTSD N=26 30mg: 7 75mg: 7 125mg: 12	Suicidal ideation: 1 Depression: 1	—	—	Premature ventricular contraction: 1	—	—	—	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
Mitchell, 2021[9] PTSD N=90 (46 vs 44)	Anxiety: 3 (6.5%) vs 0 Restlessness: 7 (15.2%) vs 0 Distress/panic/ stress: 4 (8.7%) vs 0 Suicidal ideation: 3 (6.5%) vs 5 (10.9%) Substance use: 3 (6.5%) vs 0 Feeling jittery: 5 (10.9%) vs 0 Intrusive thoughts: 4 (8.7%) vs 0	Drowsiness: 3 (6.5%) vs 0	Visual impairment/ disturbance: 4 (8.7%) vs 1 (2.3%) Dizziness: 6 (13%) vs 2 (4.5%) Nystagmus: 6 (13%) vs 0 Mydriasis/ dilated pupils: 7 (15.2%) vs 0	Rise in blood pressure: 5 (10.9%) vs 0	—	Nausea: 14 (30.4%) vs 5 (11.4%) Vomiting: 4 (8.7%) vs 0 Reduced/ lack of appetite: 24 (52.2%) vs 5 (11.4%)	Muscle twitching: 3 (6.5%) vs 0 Jaw clenching/ tight jaw: 6 (13%) vs 1 (2.3%) Muscle tension: 29 (63%) vs 5 (11.4%) Pain: 4 (8.7%) vs 0 Non-cardiac chest pain: 5 (10.9%) vs 1 (2.3%)	Perspiration: 9 (19.6%) vs 1 (2.3%) Sensitivity to cold/feeling cold: 9 (19.6%) vs 3 (6.8%) Dry mouth: 5 (10.9%) vs 2 (4.5%) Pollakiuria/ frequent urination: 4 (8.7%) vs 1 (2.3%) Fever: 3 (6.5%) vs 1 (2.3%) Chills: 3 (6.5%) vs 0

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
								Urinary urgency: 3 (6.5%) vs 0
Ot'alora, 2018[15] PTSD N=28 40mg: 6 100mg: 9 125mg: 13	Anxiety: • 40mg: 0 • 100mg: 3 (33.3%) • 125mg: 4 (30.8%) • Total: 7 (25%) Restlessness: • 40mg: 0 • 100mg: 1 (11.1%) • 125mg: 0 • Total: 1 (3.6%) Distress/panic/ stress: • 40mg: 0 • 100mg: 0 • 125mg: 1 (7.7%) • Total: 1 (3.6%) Depression (TEAE): • 40mg: 0 • 100mg: 2 (22.2%) • 125mg: 2 (15.4%)	—	—	—	—	—	—	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
	• Total: 4 (14.3%) Irritability (TEAE): • 40mg: 0 • 100mg: 2 (22.2%) • 125mg: 1 (7.7%) • Total: 3 (10.7%) Rumination/ increased private worries (TEAE): • 40mg: 0 • 100mg: 1 (11.1%) • 125mg: 1 (7.7%) • Total: 2 (7.1%)							
Jardim, 2021[32] PTSD N=3	Anxiety: 7 Fear: 7 Distress/panic/ stress: 3 Depression: 2 Irritability: 2 Anguish: 21	Insomnia: 1 Drowsiness: 2 Fatigue: 9 Nightmares: 3 Sleeplessness: 1	Dizziness: 2	—	Nasal congestion: 1 Shortness of breath: 1 Cough: 11	Nausea: 2 Diarrhea: 1	Headache: 6 Jaw clenching/ tight jaw: 1 Muscle tension: 1 Pain: 6	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
	Colic: 7 Rage: 3 Sadness: 6 Stress: 1 Rumination/ increasing private worries: 1 Despair: 2 Frustration: 1 Crying: 1						Non-cardiac chest pain: 1 Somatic pains: 22 Impotence: 2 Lack of libido: 1 Lack of trust: 1 Loneliness: 2 Vulnerability: 3	
Wang, 2021[34] PTSD N=37	Anxiety: 12 (32%) Suicidal ideation: 10 (27%)	Insomnia: 13 (35%) Fatigue: 10 (27%)	Visual impairment/ disturbance: 4 (11%) Dizziness: 7 (19%)	Palpita-tions/ tachycardia: 5 (14%)	—	Nausea: 11 (30%) Reduced/ lack of appetite: 5 (14%)	Headache: 25 (68%) Pain in jaw: 4 (11%) Muscle tension: 18 (49%)	Hyperhidrosis: 4 (11%)

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
			Nystagmus: 8 (22%) Vision blurred: 4 (11%) Paresthesia/ tingling sensation: 4 (11%)			Abdominal discomfort: 5 (14%)		
NCT01689740[44] PTSD N=10	Anxiety: • Lead in: 1/2 (50%) • Active placebo: 0/3 • Full dose 1: 4/7 (57.14%) • Full dose 2: 0/2 Suicidal ideation: • Lead in: 0/2 • Active placebo: 0/3 • Full dose 1: 1/7 (14.29%) • Full dose 2: 0/2 Depression: • Lead in: 0/2 • Active placebo: 0/3	Insomnia: • Lead in: 1/2 (50%) • Active placebo: 0/3 • Full dose 1: 0/7 • Full dose 2: 0/2	Tremor: • Lead in: 0/2 • Active placebo: 0/3 • Full dose 1: 0/7 • Full dose 2: 1/2 (50%) Dizziness: • Lead in: 0/2 • Active placebo: 0/3 • Full dose 1: 2/7 (28.57%) • Full dose 2: 0/2	—	Upper respiratory infection: • Lead in: 1/2 (50%) • Active placebo: 0/3 • Full dose 1: 1/7 (14.29%) • Full dose 2: 0/2 Shortness of breath (asthma): • Lead in: 1/2 (50%)	Nausea: Lead in: 0/2 Active placebo: 0/3 Full dose stage 1: 1/7 (14.29%) Full dose stage 2: 0/2 Intestinal obstruction: Lead in: 0/2 Active placebo: 0/3 Full dose stage 1: 1/7 (14.29%)	Headache: Lead in: 0/2 Active placebo: 0/3 Full dose 1: 1/7 (14.29%) Full dose 2: 0/2	Fever: Lead In: 1/2 Active placebo: 0/3 Full dose 1: 1/7 (14.29%) Full dose 2: 0/2 Skin hypersensitivity: Lead in: 0/2 Active placebo: 0/3 Full dose 1: 0/7 Full dose 2: 1/2 (50%)

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
	• Full dose 1: 1/7 (14.29%) • Full dose 2: 0/2 Anger: • Lead in: 0/2 • Active placebo: 0/3 • Full dose 1: 0/7 • Full dose 2: 1/2 (50%) PTSD: • Lead in: 0/2 • Active placebo: 0/3 • Full dose 1: 0/7 • Full dose 2: 1/2 (50%) Major depression: • Lead Iin: 0/2 • Active placebo: 0/3 • Full dose 1: 1/7 (14.29%) • Full dose 2: 0/2				• Active placebo: 0/3 • Full dose 1: 0/7 • Full dose 2: 0/2 Oropharynge-al pain: • Lead in: 1/2 (50%) • Active placebo: 0/3 • Full dose 1: 0/7 • Full dose 2: 0/2 Influenza: • Lead in: 0/2 • Active placebo: 1/3 (33.33%)	Full dose stage 2: 0/2		Exposure to violent event: Lead in: 0/2 Active placebo: 0/3 Full dose 1: 0/7 Full dose 2: 1/2 (50%)

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
					• Full dose 1: 1/7 (14.29%) • Full dose 2: 0/2			
NCT01958593[45] PTSD N=6	Anxiety: • Placebo: 0/2 • MDMA 1: 2/4 (50%) • MDMA 2: 0/2 Restlessness: • Placebo: 0/2 • MDMA 1: 1/4 (25%) • MDMA 2: 0/2 Distress/panic/stress: • Placebo: 1/2 (50%) • MDMA 1: 1/4 (25%) • MDMA 2: 0/2 Dissociation/ depersonalization/ derealization/detach-ment: • Placebo: 1/2 (50%) • MDMA 1: 0/4	Insomnia: • Placebo: 0/2 • MDMA 1: 1/4 (25%) • MDMA 2: 0/2 Fatigue: • Placebo: 0/2 • MDMA 1: 1/4 (25%) • MDMA 2: 0/2	Paresthesia/ tingling sensation: • Placebo: 0/2 • MDMA 1: 1/4 (25%) • MDMA 2: 0/2	—	—	Nausea: • Placebo: 0/2 • MDMA 1: 1/4 (25%) • MDMA 2: 0/2	Headache: • Placebo: 0/2 • MDMA 1: 1/4 (25%) • MDMA 2: 0/2 Jaw clenching/ tight jaw: • Placebo: 0/2 • MDMA 1: 1/4 (25%) • MDMA 2: 0/2 Muscle tension: • Placebo: 0/2	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
	• MDMA 2: 0/2 Low mood: • Placebo: 0/2 • MDMA 1: 2/4 (50%) • MDMA 2: 0/2 Intentional self-injury: • Placebo: 1/2 (50%) • MDMA 1: 0/4 • MDMA 2: 1/2 (50%)						• MDMA 1: 1/4 (25%) • MDMA 2: 0/2 Pain: • Placebo: 0/2 • MDMA 1: 1/4 (25%) • MDMA 2: 0/2 Concussion: • Placebo: 0/2 • MDMA 1: 0/4 • MDMA: 1/2 (50%)	

Notes. [a] Percentages not calculated because count/denominator are unclear. [b] "Erythema," "Pruritis," and "Rash" were combined as "skin irritation." [c] Data are presented as "125mg session/150mg session vs placebo." [d] Thirty-seven sessions had a full dose of 125 mg. Six sessions had a full dose of 150mg.
Abbreviations. AUD=alcohol use disorder; ENT=ear, nose, and throat; GI=gastrointestinal; MDMA=3,4-methylenedioxy-methamphetamine; PTSD=posttraumatic stress disorder; TEAE=treatment emergent adverse event; UTI=urinary tract infection.

Psilocybin

Author, Year **Diagnosis** **N** **Follow-up**	**Psychiatric**	**Sleep/ Fatigue**	**Neurologic/ Sensory**	**Cardiac**	**ENT/ Respiratory**	**GI**	**Musculo-skeletal**	**Other**
Pre-session								
Carhart-Harris, 2016[19] MDD N=12	Anxiety: 6 (50%)	—	—	—	—	—	—	—
Carhart-Harris, 2021[2] MDD N=59 (30 psilocybin vs 29 escitalopram) 6-week trial period	Anxiety: 0 vs 4 (14%) Feeling jittery: 2 (7%) vs 1 (3%) Feeling abnormal: 0 vs 3 (10%)	Sleep disorder: 1 (3%) vs 3 (10%) Fatigue: 2 (7%) vs 7 (24%)	—	Palpitations/ Tachycardia: 1 (3%) vs 3 (10%)	—	Nausea: 8 (27%) vs 9 (31%) Diarrhea: 1 (3%) vs 2 (7%) Vomiting: 2 (7%) vs 1 (3%)	Headache: 20 (67%) vs 15 (52%) Migraine: 3 (10%) vs 1 (3%)	Dry mouth: 0 vs 4 (14%)
During Session								
Bogenschutz, 2015[1] AUD N=10	—	—	—	—	—	Nausea: 1 (10%) Diarrhea: 1 (10%)	Headache: 5 (50%)	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
Davis, 2021[3] MDD N=27 (15 in treatment group)	Anxiety: 27 (56%) Fear: 26 (54%) "I felt frightened": 21 (44%) Distress/ panic/stress: 19 (40%) Emotional/ physical suffering: 37 (77%) Despair: 28 (58%) Feelings of despair: 23 (48%) Sadness: 38 (79%) Feel shaky inside: 30 (63%)	—	Tremor: 32 (67%)	Blood pressure event: 1 (2%) Heart rate event: 4 (8%)	—	—	Headache: 16 (33%) Pressure in chest/ abdomen: 32 (67%)	Isolation/ loneliness: 28 (58%) Feeling of isolation from people/ things: 26 (54%) "I felt isolated from everything/ everyone": 22 (46%)

Author, Year **Diagnosis** **N** **Follow-up**	**Psychiatric**	**Sleep/ Fatigue**	**Neurologic/ Sensory**	**Cardiac**	**ENT/ Respiratory**	**GI**	**Musculo-skeletal**	**Other**
	Grief: 29 (60%)							
Carhart-Harris, 2021[2] MDD N=59 (30 psilocybin vs 29 escitalopram)	—	—	—	—	—	Nausea: 4 (13%) vs 0	Headache: 13 (43%) vs 5 (17%)	—
Carhart-Harris, 2016[19] MDD N=12	Anxiety: 6 (50%) Confusion: 9 (75%) Paranoia: 2 (16.7%)	—	—	—	—	Nausea: 3 (25%)	Headache: 4 (33.3%)	—
Johnson, 2014[40] Tobacco addiction N=15	Fear, fear of insanity, feeling trapped: 5 (33.3%)	—	—	—	—	—	—	—

Author, Year **Diagnosis** **N** **Follow-up**	**Psychiatric**	**Sleep/ Fatigue**	**Neurologic/ Sensory**	**Cardiac**	**ENT/ Respiratory**	**GI**	**Musculo-skeletal**	**Other**
Post-session								
Bogenschutz, 2015[17] AUD N=10 Follow-up: 1 day	—	Insomnia: 1 (10%)	—	—	—	—	—	—
Davis, 2021[3] MDD N=27 (15 in treatment group) Follow-up: 2 weeks	—	Nightmares (post-session 2): 1 (4%)	Visual impairment/ Disturbance (post-session 1): 1 (4%) Visual impairment/ Disturbance (post-session 2): 2 (8%)	—	—	—	Headache (post-session 1): 7 (29%) Headache (post-session 2): 7 (29%) Physical discomfort (post-session 1): 1 (4%) Muscle tension (post-session 2): 2 (8%) Non-cardiac chest pain (post-session 2): 1 (4%)	Somatic sensations: (post-session 2): 1 (4%)

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
							Muscle twitching: (post-session 1): 1 (4%)	
Gukasyan, 2022[4] MDD N=24 Follow up: 3 months	—	—	1-min episode of visual distortions: 1 (4.2%)	—	—	—	—	—
Johnson, 2014[40] Tobacco Addiction N=15 Follow up: NR	—	—	—	—	—	—	Headache: 8/10 (80%) [a]	—
Total/timing Unspecified								
Carhart-Harris, 2018[20] MDD N=20	Anxiety: 15 (75%) Paranoia: 3 (15%)	—	Autobio-graphical visions: 14 (70%)	—	—	Nausea: 5 (25%)	Headache: 8 (40%)	—

Author, Year Diagnosis N Follow-up	Psychiatric	Sleep/ Fatigue	Neurologic/ Sensory	Cardiac	ENT/ Respiratory	GI	Musculo-skeletal	Other
Moreno, 2006[26] OCD N=9	—	—	—	Transient hypertension: 1 (11.1%)	—	—	—	—

Abbreviations. ENT=ear, nose, and throat; GI=gastrointestinal; MDD=major depressive disorder; NR=not reported; OCD=obsessive compulsive disorder.
Notes. [a] Mean onset was 6.2 hours.

QUALITY ASSESSMENT OF INCLUDED PRIMARY STUDIES

RCTs – RoB 2 Tool

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Some Concerns)
Bouso 2008[8]	Unclear Limited information about randomization process or allocation concealment.	Unclear Participants and investigators blinded, but no information about deviations or experiment flow.	High Only 6 (of 29) participants completed intervention prior to study termination.	Unclear Unclear level or handling of missing data.	Unclear Unclear if outcome assessors were blinded.	Low Appear to have reported all prespecified findings.	High

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Some Concerns)
Bogenschutz 2022[1]	Low Randomization through independent pharmacist	Low Participants and investigators blinded, although 90%+ guessed assignment correctly. No deviation from assignments.	Low 98% received first medication session, 82% received second medication session.	Low Analyzed 98% of randomized participants. Missing values imputed with multivariate imputation.	Low Outcome assessors blinded, but 90%+ guessed assignment correctly.	Low Appear to have reported all prespecified findings	Low
Mitchell 2021[9]	Low Randomization blinded through centralized web-based system	Low Participants and investigators blinded. No deviation from assignments.	Low 87–98% of participants completed 1st, 2nd, and 3rd sessions. Patients required to discontinue medications prior to study.	Unclear Omitted withdrawals from data set for 2nd (93% complete) and 3rd session (88% complete)	Low Outcome assessors blinded	Low Appear to have reported all prespecified findings	Some concerns
Carhart-Harris 2021[2]	Low Randomization by independent staff members. Baseline characteristics balanced except alcohol use.	Unclear Participants and investigators blinded. Unclear if there were deviations from assignment, no participant flow diagram.	Unclear 86% of participants adhered to intervention. 39% discontinued medications and 7% discontinued psychotherapy.	Unclear Unclear level of missing data. No imputation for missing data.	Unclear Unclear if outcome assessors were blinded.	Low Appear to have reported all prespecified findings	Some concerns

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Some Concerns)
Davis 2021[3] & Gukasyan 2022[4]	Low Randomization described, performed by investigator not involved in enrollment and screening. No baseline differences between groups.	Unclear Participants and investigators unblinded because of delayed treatment. No deviations from assignment.	Low 88% received adhered to intervention. All patients required to discontinue medications prior to study.	Low No primary outcome data were missing.	Low Outcome raters blinded to treatment status.	Low Appear to have reported all prespecified findings	Low
Dos Santos 2021[16]	Unclear "simple" randomization performed by independent researcher. Unclear balance of baseline characteristics.	Unclear Participants and investigators blinded. Unclear if deviations from assignment.	Low 100% adhered to intervention. Patients discontinued medications prior to study.	Unclear 82% had complete data for analysis	Unclear Outcomes were self-reported and 100% guessed group assignment.	Low Appear to have reported all prespecified findings	Some concerns
Glue 2016[7]	Unclear Randomization described. Allocation concealment not described. Baseline characteristics not presented.	Unclear Participants and investigators blinded. Unclear if deviations from assignment.	Unclear No description of adherence, but single-dose so likely high. All patients switched to morphine prior to study.	Unclear Unclear level and handling of missing data.	Low Participants blinded for self-reported outcomes.	Low Appear to have reported all prespecified findings	Some concerns

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Some Concerns)
Mithoefer 2019[13]	Low Randomization described and similar across studies. No significant differences in baseline characteristics.	Low Participants and investigators blinded. No deviation from assignments.	Low 7.6% dropout rate, 6/105 terminated early but completed at least 1 session and follow-up assessment. 91% took supplemental dose.	Unclear Missing data not imputed. From individual studies, 15% and lower	Low Outcome raters were masked to intervention assignment.	Low Appear to have reported all prespecified findings	Low
Mithoefer 2011[10] & 2013[11]	Unclear Randomization described. Allocation concealment not described. Most baseline characteristics similar except # months of prior therapy.	Low Participants and investigators blinded. No deviation from assignment in initial phase.	Unclear 87% received allocated intervention. 27% in the intervention group got an additional dose as a protocol amendment. All patients received non-drug therapy and discontinued medications prior to study.	Unclear All patients who completed treatment had outcome data (87%).	Low Outcome raters were masked to records of treatment sessions.	Low Appear to have reported all prespecified findings	Some concerns

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Some Concerns)
Mithoefer 2018[12]	Low Randomization and allocation concealment described. Some differences in baseline characteristics, likely due to small sample size.	Low Investigators, participants, and outcome raters masked until primary endpoint. Blind broken after primary endpoint.	Low 2/26 patients discontinued treatment. All patients received psychotherapy and discontinued other medications prior to study.	Low All patients completed primary assessment and 24/26 completed 12-month follow-up	Low Outcome raters were masked to dosage for primary assessment.	Low Appear to have reported all prespecified findings	Low
Oehen 2013[14]	Unclear No description of allocation process. No significant differences between groups at baseline.	Low Double blind study until open label arm. No reported deviations from assignment.	Low Few participants continued on to the open label phase (T3 and beyond), but results are only provided for T1 and T2, representing the full sample. 2 participants withdrew after first dose due to AEs.	Unclear Excluded data from 2/14 (15%) of sample.	Low Outcomes were assessed by blinded study staff. Investigators provided guesses on condition assessments with an accuracy rate of 59%, indicating that blinding was effective.	Low Results appear to follow pre-specified analysis plan.	Some concerns

Author Year	Risk of Bias from Randomization Process	Risk of Bias from Deviation from Intended Interventions (Assignment)	Risk of Bias from Deviation from Intended Interventions (Adherence)	Risk of Bias from Missing Outcome Data	Risk of Bias in Measurement of Outcome	Risk of Bias in Selection of Reported Result	Overall Bias (High, Low, Some Concerns)
Ot'alora 2018[15]	Low Allocation was completed through a web-based system and was blinded to study staff	Low Participants and all study staff were blinded to assignment until open label phase	Unclear 5/28 (18%) did not complete intervention	Low Data from 1 participant who withdrew was excluded.	Low Outcomes were measured by blinded independent raters.	Low Appear to have reported all prespecified findings	Some concerns
Palhano-Fontes 2019[5] & Zeifman 2019[6]	Unclear Allocation via permuted blocks of size 10. Zeifman 2019 describes low suicidality in placebo group despite randomization. Intervention assignment was stored in database and only known to pharmacy administrators.	Low All investigators and patients were blind to intervention. Each patient was assigned a different blinded psychiatrist for each dosing session.	Unclear 17% didn't receive intervention. Investigators and participants blinded with placebo participants were given a substance that resembled ayahuasca and produced GI distress. Participants with past ayahuasca use were excluded to enhance intervention blindness.	Low Several patients did not meet criteria after washout and were excluded from analysis. 1 patient dropped out of study. Missing data imputed.	Unclear Psychiatrists' blindness was not assessed, but they were randomly assigned to each patient each dosage session. Zeifman 2019 does not clarify if clinicians administering MADRS were blinded to assignment.	Low Results appear to follow pre-specified analysis plan.	Some concerns

Abbreviations. AE=adverse event; GI=gastrointestinal; MADRS=Montgomery-Asberg Depression Rating Scale; T1/2/3=timepoint 1/2/3.

Observational Studies – ROBINS-I Tool for Cohort Studies

Author Year	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended Intervention	Bias Due to Measurement of Outcomes	Bias Due to Confounding	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (High, Low, Unclear)
Lyons 2018[21]	Unclear Control group matched on age, gender, and education, and was assessed over a similar timeframe, but minimal information about how patients were selected into study.	Unclear Intervention clearly defined. Unclear what (if anything) controls received - says "untreated."	Unclear No information on patient adherence or if controls received any type of intervention during the period.	Unclear Self-reported depression measures may have been influenced by knowledge of intervention.	High Control group differed significantly from intervention group in baseline depression. Matched on other factors, but for outcome of depression there is high risk of confounding.	Unclear Unclear level and handling of missing data	Unclear No protocol identified.	High
Stroud 2018[25]	High Minimal information about control group. Controls had no psychiatric illness and likely differed from those in the trial which comprised the intervention group.	Unclear Intervention clearly defined. Unclear what (if anything) controls received.	Unclear No information on patient adherence or if controls received any type of intervention during the period.	Unclear Self-reported depression measures may have been influenced by knowledge of intervention.	High Minimal information about control group and likely that they differed from intervention group. No adjustment for confounding.	High Missing data handled with likewise deletion. Unclear level of missing data.	Unclear No protocol identified.	High

Observational Studies – ROBINS-I Tool for Uncontrolled Pre-post Studies

Author Year	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended intervention	Bias Due to Measurement of Outcomes	Bias Due to Confounding	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (High, Low, Unclear)
Bogenschutz 2015[17]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined.	Unclear 3/10 patients didn't complete 2nd psilocybin session	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Low Omitted missing data, but low level	Unclear No protocol identified	High
Brown 2018[27]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined.	Unclear No information on adherence, but likely high since it was a single administration.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear Did analyses either omitting missing data or setting it to baseline values. Unclear level of missing data.	Unclear No protocol identified	High
Carhart-Harris 2016[19], 2018[20]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear No information on adherence. Intensive preparatory visit prior to psychedelic visit.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Low All patients completed measures	Unclear No protocol identified	High

Author Year	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended intervention	Bias Due to Measurement of Outcomes	Bias Due to Confounding	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (High, Low, Unclear)
Davis 2017[28]	Low Same groups of patients followed for pre-post assessments	High Pre- and post-assessment were done at the same time through a survey.	Unclear No information on intervention adherence, only that they had received treatment during a certain time period.	High Measures self-reported and collected pre- and post-measure both post-intervention in a single survey.	High Single pre-treatment measurement. No analysis of potential confounders.	Low Table 1 indicates that they had data for all but 1 participant.	Unclear No protocol identified	High
Davis 2020[42]	Low Same groups of patients followed for pre-post assessments	High Pre- and post-assessment were done at the same time through a survey.	Unclear No information on intervention adherence, only that they had received treatment during a certain time period.	High Measures self-reported and collected pre- and post-measure both post-intervention in a single survey.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear Unclear level and handling of missing data.	Unclear No protocol identified	High
Jardim 2021[32]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear 3 patients, all completed program. Several pre-intervention sessions.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Low Appears data were available for all patients.	Unclear No protocol identified	High

Author Year	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended intervention	Bias Due to Measurement of Outcomes	Bias Due to Confounding	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (High, Low, Unclear)
Johnson 2014[40] & 2017[41]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear 12/15 completed all 3 sessions. Program also involved CBT.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Low Appears data were available for all patients.	Unclear No protocol identified	High
Knuijver 2022[29]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Low All patients completed study	Low Outcome assessment similar pre and post intervention. Outcomes were clinician assessed.	High Single pre-treatment measurement. No analysis of potential confounders.	Low Appears data were available for all patients.	Unclear No protocol identified	High
Malcolm 2018[30]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear No information on intervention adherence.	Low Outcome assessment similar pre and post intervention. Outcomes were clinician assessed.	Unclear Two pre-treatment measures and multiple post-treatment measures. No assessment of confounders.	Unclear Omitted missing data from 10/50 patients on baseline demographics.	Unclear No protocol identified	Unclear

Author Year	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended intervention	Bias Due to Measurement of Outcomes	Bias Due to Confounding	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (High, Low, Unclear)
Mash 2001[37]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear No information on intervention adherence.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear Unclear level and handling of missing data.	Unclear No protocol identified	High
Mash 2000[36]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear No information on intervention adherence.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear Unclear level and handling of missing data.	Unclear No protocol identified	High
Mash 2018[38]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear No information on intervention adherence.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear Unclear level and handling of missing data.	Unclear No protocol identified	High

Author Year	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended intervention	Bias Due to Measurement of Outcomes	Bias Due to Confounding	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (High, Low, Unclear)
Monson 2020[33]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Low All couples completed the protocol. Intervention included CBCT therapy	Low Outcome assessment similar pre and post intervention. Outcomes clinician assessed.	High Single pre-treatment measurement. No analysis of potential confounders.	Low No missing data for clinician-assessed PTSD data. Overall assessment completion 86%.	Unclear No protocol identified	High
Moreno 2006[26]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear 2/9 did not complete study. 6/9 received all doses.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear Unclear level and handling of missing data.	Unclear No protocol identified	High
Noller 2018[31]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Low 14/15 completed treatment.	Unclear Outcome assessment changed over time (in-person, over the phone, mailed surveys).	High Single pre-treatment measurement. No analysis of potential confounders.	High (urine screen)/unclear (other outcomes) High levels of missing urine screen data. Level of missing data unclear for other outcomes, but states 14/14 were analyzed.	Unclear No protocol identified	High

Author Year	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended intervention	Bias Due to Measurement of Outcomes	Bias Due to Confounding	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (High, Low, Unclear)
Osorio 2015[22]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear No information on intervention adherence.	Low Outcome assessment similar pre and post intervention. Outcomes clinician assessed.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear Data missing for 1 patient on blood pressure measures. Unclear if there were missing data for other outcomes.	Unclear No protocol identified	High
Sanches 2016[23] & Zeifman 2021[24]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Unclear No information on intervention adherence.	Low Outcome assessment similar pre and post intervention. Outcomes clinician assessed.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear No information on level and handling of missing data.	Unclear No protocol identified	High
Schenberg 2014[39]	Low Same groups of patients followed for pre-post assessments	Unclear Unclear how long since intervention the interviews were conducted.	Unclear Unclear if patients adhered to planned intervention.	High Measures assessed after intervention. Non-patients were interviewed in almost 20% of cases.	High Appears that pre-treatment use was assessed in post-treatment interview.	Unclear No information on level and handling of missing data.	Unclear No protocol identified	High

Author Year	Selection Bias	Bias in Classification of Interventions	Bias Due to Departures from Intended intervention	Bias Due to Measurement of Outcomes	Bias Due to Confounding	Bias Due to Missing Data	Bias in the Selection of Reported Results	Overall Bias (High, Low, Unclear)
Sessa 2021[43]	Low Same groups of patients followed for pre-post assessments	Low Time points for pre- and post-assessments clearly defined	Low 12/14 received both sessions.	Low Outcome assessment similar pre and post intervention. Outcomes clinician assessed.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear Mean data used for missing data. 4/14 had missing data for 1 question on SADQ.	Unclear No protocol identified	High
Thomas 2013[35]	Unclear Data came from 2 different retreats.	Low Time points for pre- and post-assessments clearly defined	Unclear 3/18 did not complete retreat. Unclear adherence to all aspects of retreat.	Unclear Outcome assessment similar pre and post intervention. Outcome self-reported may be influenced by study participation.	High Single pre-treatment measurement. No analysis of potential confounders.	Unclear 3/18 with missing data excluded from analysis.	Unclear No protocol identified	High
Wang 2021[34]	Low Same groups of patients followed for pre-post assessments.	Low Time points for pre- and post-assessments clearly defined.	Unclear Describes mean # of sessions, but unclear adherence to all sessions.	Low Outcome assessment similar pre and post intervention. Outcomes clinician assessed.	High Single pre-treatment measurement. No analysis of potential confounders.	Low 1/37 did not complete primary endpoint assessment.	Unclear No protocol identified	High

Abbreviations. CBCT=cognitive-behavioral conjoint therapy; CBT=cognitive behavioral therapy; PTSD=posttraumatic stress disorder; SADQ=Severity of Alcohol Dependence Questionnaire; SUD=substance use disorder.

STRENGTH OF EVIDENCE FOR INCLUDED STUDIES

Outcome	Psychedelic	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
Alcohol Use Disorder								
Drinking behavior	Psilocybin	Bogenschutz 2022,[1] Bogenschutz 2015[17]	Low to high	Direct	Consistent	Imprecise	Unknown	Low Psilocybin may decrease drinking behavior based on an RCT and pre-post study.
Drinking behavior	MDMA	Sessa 2021[43]	High	Direct	Unknown	Unknown	Unknown	Insufficient It is unclear whether MDMA decreases drinking behavior based on a single pre-post study.
Major Depressive Disorder								
Depressive symptoms	Psilocybin	Carhart-Harris 2016[19], Carhart-Harris 2018[20], Davis 2021[3], Gukasyan 2022[4], Lyons 2018[21], Stroud 2018[25]	Low to high	Direct	Consistent	Imprecise	Unknown	Low Psilocybin with psychotherapy may reduce depressive symptoms compared to no treatment, based on a single RCT and 3 pre-post studies with small sample sizes.
Depressive symptoms	Psilocybin	Carhart-Harris 2021[2]	Moderate	Direct	Unknown	Imprecise	Unknown	Low Psilocybin-assisted psychotherapy may not reduce depressive symptoms compared to psychotherapy and daily escitalopram.

Outcome	Psychedelic	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
Depressive symptoms	Ayahuasca	Palhano-Fontes 2019,[5] Osorio 2015[22], Sanches 2016[23], Zeifman 2021[24]	Moderate to high	Direct	Consistent	Unknown	Unknown	Low Ayahuasca may reduce depressive symptoms based on a single RCT and 2 pre-post study with small sample sizes.
Suicidal ideation	Psilocybin	Carhart-Harris 2021[2]	Moderate	Direct	Unknown	Imprecise	Unknown	Insufficient It is unclear whether psilocybin improves suicidal ideation compared to escitalopram based on a single RCT.
Suicidal ideation	Psilocybin	Davis 2021[3], Gukasyan 2022[4]	Low	Direct	Unknown	Imprecise	Unknown	Insufficient It is unclear whether psilocybin improves suicidal ideation based on a single RCT compared to delayed treatment.
Suicidal ideation	Ayahuasca	Palhano-Fontes 2019,[5] Zeifman 2019,[6] Sanches 2016,[23] Zeifman 2021[24]	Moderate to high	Direct	Consistent	Imprecise	Unknown	Insufficient Ayahuasca may improve suicidal ideation over time, but it is unclear whether it differs from placebo based on a single RCT and a single pre-post study with small sample sizes.

Outcome	Psychedelic	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
Opioid Use Disorder								
Opioid use	Ibogaine	Davis 2017[28], Brown 2018[27], Noller 2018[31], Glue 2016[7]	High	Direct	Consistent	Unknown	Unknown	Low Ibogaine may reduce opioid use immediately after treatment, but limited by pre-post studies with high RoB. Single RCT showed similar time to resumption of opioid substitution therapy among participants on methadone.
Withdrawal	Ibogaine	Davis 2017[28], Brown 2018[27], Knuijver 2022[29], Malcom 2018[30], Noller 2018[31], Glue 2016[7]	High	Direct	Consistent	Unknown	Unknown	Low Ibogaine may reduce opioid withdrawal symptoms immediately after treatment, but limited by pre-post studies with mostly high RoB. Single RCT showed increases in withdrawal symptoms within 10 hours of last morphine dose among participants on methadone.
Posttraumatic Stress Disorder								
Remission	MDMA	Mitchell 2021[9], Mithoefer 2011[10], Mitheofer 2018[12], Ot'alora 2018[15]	Low - some concerns	Direct	Consistent	Unknown	Unknown	Low: MDMA-assisted psychotherapy may result in PTSD remission compared to placebo based on 4 RCTs.

Outcome	Psychedelic	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
Clinically meaningful improvement	MDMA	Mitheofer 2011[10], Mithoefer 2018[12], Ot'alora 2018[15], Oehen 2013[14]	Low - some concerns	Direct	Consistent	Unknown	Unknown	Low: MDMA-assisted psychotherapy may result in a clinically meaningful reduction in symptom burden (defined as a >30% improvement on CAPS total severity scores) compared to placebo based on 4 RCTs.
Change in mean symptom scores	MDMA	Mitchell 2021[9], Mithoefer 2011[10], Mitheofer 2018[12], Ot'alora 2018[15], Oehen 2013[14], Bouso 2008[8], Jardim 2021[32], Monson 2020[33], Wang 2021[34], NCT01958593[45], NCT01689740[44]	Low to high	Direct	Consistent	Imprecise	Unknown	*Low SOE:* MDMA-assisted psychotherapy may reduce PTSD symptoms (in 7 trials, the pooled mean difference in PTSD symptom change for intervention dose MDMA compared with 0mg or low-dose placebo is -18.0 (95% CI [-30.0, -6.0]).
Tobacco Use								
Tobacco Use	Psilocybin	Johnson 2014[40], Johnson 2017[41]	High	Direct	Unknown	Unknown	Unknown	Insufficient It is unclear whether psilocybin influences tobacco use based on a single pre-post study.

Outcome	Psychedelic	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
Mixed Substance Use								
Substance use	Ayahuasca	Thomas 2013[35]	High	Direct	Unknown	Unknown	Unknown	Insufficient It is unclear whether ayahuasca reduces substance use in participants of a substance use program based on a single study.
Opiate and cocaine craving	Ibogaine	Mash 2000,[36] Mash 2001,[37] Mash 2018[38]	High	Direct	Unknown	Unknown	Unknown	Insufficient It is unclear whether ibogaine reduces opiate and cocaine craving in participants of a substance use program based on a single study.
Substance use	Ibogaine	Schenberg 2014[39]	High	Direct	Unknown	Unknown	Unknown	Insufficient It is unclear whether ibogaine reduces substance use in participants of a substance use program based on a single study.
Other Conditions								
Mood and anxiety symptoms	Ibogaine	Davis 2020[42]	High	Indirect	Unknown	Unknown	Unknown	Insufficient It is unclear whether ibogaine reduces mood and anxiety symptoms in US special operations forces based on a single study.
Social anxiety symptoms	Ayahuasca	Dos Santos 2021[16]	Some concerns	Indirect	Unknown	Unknown	Unknown	Insufficient It is unclear whether ayahuasca improves social anxiety symptoms based on a single pre-post study.

Outcome	Psychedelic	Studies	Study Limitations	Directness	Consistency	Precision	Reporting Bias	Rating and Summary of Evidence
OCD Symptoms	Psilocybin	Moreno 2006[26]	High	Direct	Unknown	Unknown	Unknown	Insufficient It is unclear whether psilocybin impacts OCD symptoms based on a single pre-post study.

Abbreviations. MDMA=3,4-methylenedioxy-methamphetamine; OCD=obsessive compulsive disorder; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial; RoB=risk of bias; US=United States.

APPENDIX D: PEER REVIEW DISPOSITION

Comment #	Reviewer #	Comment	Author Response
Are the objectives, scope, and methods for this review clearly described?			
1	1	Yes	*None*
2	3	Yes	*None*
3	4	Yes	*None*
4	5	Yes	*None*
5	6	Yes	*None*
6	7	Yes	*None*
7	8	Yes	*None*
Is there any indication of bias in our synthesis of the evidence?			
8	1	No	*None*
9	2	No	*None*
10	3	Yes - Pg22, 5 & Pg32, 21: “but whether effects are primarily due to psilocybin exposure or intensive psychotherapy remains unclear”, can you expand on the inclusion of this statement? This doesn’t seem to address a key question of this evidence review. This statement perhaps presents a false dichotomy unnecessarily, I suggest more framing or removing.	*Thank you for this comment. We agree that this wording is problematic without additional context and have removed it. In the section pertaining to PTSD, we now discuss in more detail our assessment of what the evidence can and cannot tell us about the relative contribution of the intervention components.*
11	4	No	*None*
12	5	No	*None*
13	6	No	*None*
14	7	No	*None*
15	8	No	*None*
Are there any published or unpublished studies that we may have overlooked?			
16	1	No	
17	2	No	
18	3	Yes - Anderson BT, et al. (2020). Psilocybin-assisted group therapy for demoralized older long-term AIDS	*Thank you for identifying this study, which we did not find in our search. This study does not meet our inclusion criteria as we excluded studies of adults with serious*

Comment #	Reviewer #	Comment	Author Response
		survivor men: an open-label safety and feasibility pilot study. EClinicalMedicine. 100538.	*medical illness (eg terminal cancer, end-stage renal disease, and in this case HIV/AIDS) experiencing secondary mental health symptoms.*
19	4	No	*None*
20	5	No	*None*
21	6	No	*None*
22	7	No	*None*
23	8	No	*None*
Additional suggestions or comments can be provided below. If applicable, please indicate the page and line numbers from the draft report.			
24	1	Overall I think this is a good draft. I found it helpful to see the data summarized this way. My overarching concern is the lack of attention to the adequacy of placebo control in this research. It is a known challenge because it is difficult to plausibly mimic the effects of psychedelic drugs, e.g., https://doi.org/10.1038/s41591-021-01524-1. The limited use of active placebos and reduced adequacy of blinding tempers the evidence of effectiveness. I am commenting on the MDMA-assisted psychotherapy studies for PTSD but the issue is broadly relevant.	*Thank you for your comments regarding the use of different placebos. In the Results section pertaining to MDMA-assisted psychotherapy, we have expanded our discussion on the use of inactive (0mg) and low-dose placebos. We comment that low-dose placebos are meant to produce some of the sensations of having ingested a psychedelic but are thought to have a subtherapeutic effect that is distinct from psychedelic doses used in intervention groups. We revised Figure 3 (forest plot) to separate the studies using inactive and low-dose placebos and now provide pooled estimates for the study sub-groups. We comment that use of inactive placebos with inadequate blinding is a potential source of bias in the Results section and in the Limitations sections.*
25	1	In MDMA-assisted psychotherapy for PTSD, 2 of the 5 published studies used inactive placebo (Mithoefer et al., 2011; Mitchell et al., 2021), whereas the other studies used lose-dose MDMA: 25 mg (Oehen et al., 2013), 30 mg (Mithoefer et al., 2018), and 40 mg (Ot'alora, 2018). This is a particular problem for interventions like psychedelics, for which there is a lot of hype and public-facing "evidence" on the efficacy of these interventions.	*As stated above, we now explicitly discuss the use of 2 placebo types – 0mg placebo and low-dose placebo.*
26	1	Blinding was inadequate in the studies that used inactive placebo. In the Mithoefer et al. (2011) study, 95% of participants correctly guessed their assigned	*Thank you for your comments regarding the potential for ineffective blinding. As stated above, we comment that use of inactive placebos with inadequate blinding is a*

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		condition, and in the Mitchell study, 84%/96% guessed correctly in the inactive/MDMA groups, respectively. Guessing was less accurate in studies that used active placebo, but still incomplete: 46% overall in Mithoefer (2018); 46% vs. 66% in 25mg vs. 125 mg in Oehen (2013); and 73% vs. 58% in 40mg vs. 100/125 mg in Ot'alora (2018). Even if the effect sizes in the ESP report do not vary as a function of blinding—and for MDMA I think they probably do not due to the Mitchell study having a relatively small effect and the Mithoefer 2018 study having a large effect—this is a key issue that should be addressed in the report to caution readers.	*potential source of bias in the Results section and in the Limitations sections. We also recommend use of low-dose placebo in the Future Research section and recommend that studies report data on blinding effectiveness.*
27	1	Another concern is the limited number of total as well as Veteran participants that have been studied in MDMA-assisted psychotherapy for PTSD. Looking at the 5 published studies, these trials have included a total of only 176 participants in the ITT samples.* All except one study (Mitchell et al., 2021, N = 90) included fewer than 30 participants. Almost 2 out of 3 participants (64%) have been female and almost no participants have experienced combat trauma or were military veterans, with the exception of the study by Mithoefer et al. (2018), which enrolled 22 Veterans. The existing data therefore have limited generalizability to VA patients. The ongoing MAPS study (https://clinicaltrials.gov/ct2/show/NCT04077437) may mitigate this limitation, but it is unlikely that many Veterans will be enrolled given that the protocol does not focus specifically on Veterans. Effect sizes in PTSD medication and psychotherapy studies are smaller in Veteran and active duty samples relative to non-military samples, so the lack of Veteran data is likely to cause the effects on Veterans to be overestimated.	*Thank you for this comment. We added a sentence to the Key Findings in the Executive Summary to highlight the low inclusion rates of Veterans. In the Discussion and Limitations section, we comment on concerns related to generalizing study findings to VHA populations. We have also recommended inclusion of Veteran populations as a priority in the Future Research section.*
28	1	*I was surprised to see the sample sizes listed for these trials because they are smaller than those reported in the studies. I looked at one trial, Mitchell, in which the sample size is 90 overall and 89 in the primary MMRM analysis, even though data are missing for some	*Thank you for this comment. In this particular study, the outcome of change from baseline in PTSD symptoms was only reported for participants who completed the intervention, which was 79. We reviewed the report Tables and Figures for consistency and clarified when*

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		participants in later assessments. Figure 3 in the ESP report lists the N as 79; however, the authors say the N for T4, the final endpoint, was 82. So even if the ESP report is using the T4 N, it is difficult to understand how the total was 79. I assume that the language on the calculation of effect sizes is standard, but in this and future reports, it would be helpful to clarify how the Ns were determined.	*we were referencing the "analytic N" rather than the study's total N.*
29	1	Pg 1 Line 11-12: It is extremely important to present the effect sizes for the active and placebo controlled studies separately. Also, one of the major issues in this literature is the problem of unblinding in placebo control. IT is a key issue that undermines the interpretation of findings. Having just reviewed this literature carefully, I don't think this interpretation is valid given the serious limitations in the literature.	*As stated above, we now explicitly discuss the use of 2 placebo types – 0mg placebo and low-dose placebo. We revised Figure 3 (forest plot) to separate the studies using inactive and low-dose placebos and now provide pooled estimates for the study sub-groups.*
30	1	Pg 1 Line 33: What about the challenges of placebo blinding--finding credible active placebo is challenging, especially for long-acting medications like MDMA and psilocybin	*Please see responses to Comments #24-26.*
31	1	Pg 2 Line 18-19: Please see prior comments about the importance of presenting effect sizes for active and placebo control separately. This is analagous to presenting separate effect sizes for in psychotherapy studies for active and waitlist, for example. And placebo control is inadequate, so interpretation needs to be tempered.	*Please see responses to Comments #24-26.*
32	1	Pg 31 Line 48-49: This section [Discussion] needs to address the issue of placebo plinding and the need for adequate control. The possibility of plcebo effects is especially concerning for threatments like MDMA that have been promoted in the popular press	*Please see responses to Comments #24-26.*
33	1	Pg 31 Line 48-49: please see: Caution at psychiatry's psychedelic frontier. Matthew J. Burke1,2,3,4 ✉ and Daniel M. Blumberger1,5 arising from J. M. Mitchell et	*Thank you for highlighting this commentary. In the Results section pertaining to MDMA-assisted psychotherapy for PTSD, we discuss the use of different placebo types and specifically highlight that Mitchell 2021*

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		al. Nature Medicine https://doi.org/10.1038/s41591-021-01336-3 (2021)	*used an inactive placebo. As above, we recommend use of low-dose placebo in the Future Research section and recommend that studies report data on blinding effectiveness.*
34	1	Pg 31 Line 57: Two of the 5 published MDMA studies used inactive placebo (Mithoefer et al., 2011; Mitchell et al., 2021), whereas the other studies used lose-dose MDMA: 25 mg (Oehen et al., 2013), 30 mg (Mithoefer et al., 2018), and 40 mg (Ot'alora, 2018). Blinding was inadequate in the studies that used inactive placebo. In the Mithoefer et al. (2011) study, 95% of participants correctly guessed their assigned condition, and in the Mitchell study, 84%/96% guessed correctly in the inactive/MDMA groups, respectively. Guessing was less accurate in studies that used active placebo: 46% overall in Mithoefer (2018); 46% vs. 66% in 25mg vs. 125 mg in Oehen (2013); and 73% vs. 58% in 40mg vs. 100/125 mg in Ot'alora (2018). **The data indicate that active placebo is needed in order to achieve adequate blinding, which is especially important given the novelty of MDMA and the media's portrayal of its efficacy.**	*Please see responses to Comments #24-26.*
35	1	Pg. 32 Line 16-17: **Limitations of findings:** These trials have included a total of only 176 participants. All except one study (Mitchell et al., 2021, N = 90) included fewer than 30 participants. Almost 2 out of 3 participants (64%) have been female and almost no participants have experienced combat trauma or were military veterans, with the exception of the study by Mithoefer et al. (2018), which enrolled 22 Veterans. **The existing data therefore have limited generalizability to VA patients.** The ongoing MAPS study (https://clinicaltrials.gov/ct2/show/NCT04077437) may mitigate this limitation, but it is unlikely that many Veterans will be enrolled given that the protocol does not focus specifically on Veterans.	*Please see response to Comment #27.*
36	1	Pg 33 Line 39-40: active placebo-controlled studies	*Please see responses to Comments #24-26.*
37	1	Pg 33 Line 44-45: include veterans	*Please see response to Comment #27.*

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38	2	This review is thorough and comprehensive and provides a detailed overview of the full landscape of psychedelic use in MH and SUD conditions, which is much needed and appreciated. However, I am concerned that the summary of findings for MDMA for PTSD is overstating the strength of the evidence. The limitations of studies were not as fully explored in this section as I think is warranted. For example, there was little mention of the problematic nature of the 2 studies that are placebo controlled, especially given in those studies the participants had very high rates of identifying whether they received treatment or placebo (hence very high risk of being unblinded). Lumping these studies together with the active comparator studies is problematic. Also, the total N across all MDMA studies is only 176, with all but the 2021 Mitchell study having N<30. Also - there is little note of the study population of greatest interest to VA - Veterans. Most of these psychedelic studies are lacking in veteran participants, especially combat veterans (of particularly important note for PTSD studies). This is something that should be added to the discussion as well as an area needed to expand upon findings with future research.	*Thank you for these comments. Please see our responses to Comments #24-27 above, which address similar concerns raised by Reviewer 1. We reassessed our Strength of Evidence (SOE) rating for MDMA-assisted psychotherapy for PTSD (now rated as low SOE) accounting for the limitations that you and other reviewers highlighted.*
39	3	Pg2, Ln58: long-term, cite long-term MDMA studies clearly	*We have removed this sentence from the Executive Summary to improve clarity. In our discussion of evidence gaps and areas for future research, we include the durability of treatment effects as a gap.*
40	3	Pg6, 41: “expectations” should maybe be changed to “intentions”? (a tenet of this intervention is "intention without expectation", i.e., expectation/expectancy is a component of 'set' that is mitigated)	*Change made.*
41	3	P6,58: comma after “feasibility”	*Change made*
42	3	Pg11, 29: Mitchell used CAPS-5, which has a different score range	*We have corrected the text regarding CAPS-5 scoring.*
43	3	Pg13, 53: consider making it clear that participants were able to continue psychotherapy with outside provider(s) during study participation	*Thank you for this comment. In the Results section, we now provide more detail (when reported by individual studies) on how many study participants continued or*

Comment #	Reviewer #	Comment	Author Response
			restarted other treatments during the study period or follow-up period.
44	3	Pg24, 51: "3-4 integration sessions"; the protocol from Mitchell (2021) included 9 integration sessions total and many Phase 2 MDMA studies included 6-9 integration sessions	*We had originally counted only the sessions that were not aligned with the experimental sessions. We have revised the wording to reflect the total number of sessions.*
45	3	Pg32, 27: edit "estimate draw conclusions"	*Removed "estimate"*
46	4	Thank you for the opportunity to review this ESP. I found the summary to be thorough in highlighting the limitations of current psychedelic research (which includes small size of trials, inconsistency in intervention and co-intervention, risk of bias, limitations in blinding, and lack of data on long-term durability). The recommendations for future research are prudent, as preliminary data is positive. The clinical implication of discontinuing current treatment is certainly relevant as more people seek these compounds worldwide and standard treatments are lacking.	*Thank you for your comments.*
47	5	The authors conducted a systematic review of studies examining the effects of psychedelic medications for mental health and substance use disorders. They included 38 studies. They found moderate strength evidence indicating that MDMA likely improves PTSD symptoms. The strength of evidence for the remaining effects were deemed either low or insufficient.	*None*
48	5	This is a very well written and comprehensive review of the literature. In my view, the authors provided a balanced portrayal and contextualized their findings as applied to the veteran population nicely. I have a few suggestions they might consider addressing.	*Thank you for your comments. Suggestions are addressed below.*
49	5	I wonder if it would be helpful to spend a bit more time discussing the content of the psychotherapy component of the psychedelic-assisted psychotherapies. A brief description of this treatment component is included in Table 2 but was discussed only briefly in the text. A better understanding of what this psychotherapy component entails may be helpful for stakeholders, particularly given issues related to accessibility and	*We agree and have expanded our discussion of the psychotherapy component of the interventions for PTSD and depression in particular.*

Comment #	Reviewer #	Comment	Author Response
		scalability which were highlighted. For example, how equipped might VA mental health providers / systems be to deliver the interventions that are being tested in these trials?	
50	5	I may have missed this, but I was curious what sample size cutoff was used to evaluate whether a trial was small or not for the purposes of grading the strength of evidence. In particular, I was curious why the Carhart-Harris et al. (2021) psilocybin for depression trial (n = 59) provided insufficient evidence. In comparison, the authors graded evidence from the Davis et al. (2020) trial (n = 27) when combined with 4 pre-post studies as providing low strength of evidence (i.e., not insufficient).	*Thank you for this comment. We reassessed our Strength of Evidence (SOE) ratings for the outcomes related to depression to be consistent with the algorithm we presented in the Methods section ("low strength evidence consisted of a single trial or multiple small trials and/or multiple observational studies, with unclear to high risk of bias, consistent findings, and clinically relevant outcomes"). In this case, we rated the SOE as low for the outcomes informed by the Carhart-Harris 2021 trial and the Davis 2020 trial.*
51	5	I realize this may not be typically done for VA ESP reviews, but I wondered whether it would be helpful to calculate standardized effect sizes for those studies that reported mean differences (e.g., MDMA for PTSD, Carhart-Harris et al., 2020). From my perspectives, effect sizes provide another helpful metric of potential magnitude of effects beyond the grading of the strength of evidence.	*Thank you for this comment. Given this and other reviewers' feedback, we have calculated SMDs for CAPS outcomes of MDMA for PTSD studies.*
52	5	I wondered about the authors' choice to combine MDMA trials that included placebo and active controls. In general, I think it is much preferred to avoid combining across control condition types. At the very least, the authors might discuss why this is appropriate (e.g., active control MDMA dose was too low to be considered therapeutic and/or unlikely to produce a perceptible effect). Might it be possible to examine whether control condition type moderated treatment effects?	*Thank you for these comments. Please see our responses to Comments #24-25 above, which address similar concerns raised by Reviewer 1. We revised Figure 3 (forest plot) to separate the studies using 0mg and low-dose placebos and now provide pooled estimates for the study sub-groups.*
53	5	Two potential typos to correct: p. 2, line 60 ("PTSD-assisted psychotherapy -> "psychedelic-assisted psychotherapy"), p. 11, line 35 ("PI" -> "CI").	*"PTSD-assisted" has been changed to "psychedelic-assisted". "PI" is correct as it is referring to the prediction interval, not the confidence interval.*
54	6	None	*None*

Comment #	Reviewer #	Comment	Author Response
55	7	This is a concisely written report summarizing the evidence to date on the use of psychedelic pharmacotherapy for the treatment of mental health and substance use disorder. The overall report was informative, accurate and portrayed a non-biased review of classic and non-classic psychedelics, with their evolution, history, structure, and proposed mechanism of action. A comprehensive review of the evidence to date on efficacy, risks and benefits was well summarized. As stated in the review, the evidence on psychedelics for the treatment of mental health and substance use disorders is insufficient or low strength in evidence for most of the psychedelics. The one caveat to this is the evidence for MDMA-assisted therapy for PTSD where research according to this report is moderately strong in favor of the benefits of MDMA for improving PSTD. While the evidence does in fact support a strong signal for the efficacy of MDMA for treating PTSD with associated serious risks being rare, there are several practical, methodological and generalizability concerns with these studies that should be made more explicit - as they potentially mitigate this favorable rating. These concerns are summarized below.	*Thank you for your comments. Suggestions are addressed below.*
56	7	The “psychotherapy” component across all the MDMA-assisted therapy studies for PTSD is vague and varies significantly in session number and likely content, except Monson et al., 2020. It is unclear if any of the strides made in PTSD psychotherapy research over the past 2 decades have been integrated into the “therapy” component of the MAPS MDMA-assisted therapy protocol for PTSD. Current MAPS protocol for preparation and integration is loosely structured and not in line with current best practice for PTSD therapy. This has significant implications for replication and implementation in settings such as VHA. Future studies examining MDMA-assisted evidence-based psychotherapy for PTSD are needed.	*Thank you for this comment. We added a paragraph to the Limitations section to discuss the lack of clarify on to what extent, if any, protocols such as those used by MAPS overlap with recommended VA/DoD psychotherapy approaches.*

Comment #	Reviewer #	Comment	Author Response
57	7	A significant methodological concern across the MDMA studies is the placebo comparator. Given the subjective experience of MDMA there is a clear placebo problem with many of these studies and this should temper enthusiasm of findings. Although this is highlighted in the review, this point should be made more explicit.	*Thank you for these comments. Please see our responses to Comments #24-25 above, which address similar concerns raised by Reviewer 1.*
58	7	Most of the published MDMA studies are small. The largest study to date is Mitchell and colleagues (2021) which was only an N=90. This is a relatively small sample size for a phase III trial and raises concern with replication in a larger more diverse samples and settings, as noted. The moderate rating would be more compelling if there were larger more diverse samples.	*Thank you for this comment. We reassessed our Strength of Evidence (SOE) rating for MDMA-assisted psychotherapy for PTSD (now rated as low SOE) accounting for the limitations that you and other reviewers highlighted.*
59	7	All MDMA studies were funded/sponsored by MAPS raising concern re bias.	*In the Result section, we state that all studies were funded or sponsored by MAPS.*
60	7	The lack of current MDMA evidence with military veterans' seeking mental health treatment in a VA setting is perhaps the largest concern. Given the medical and psychiatric complexity of the veteran mental health treatment seeking population, this is a significant gap. This current evidence cannot be generalized to this important population.	*Thank you for these comments. Please see our responses to Comment #27 above, which address similar concerns raised by Reviewer 1.*
61	7	Given these important concerns I believe a strong cautionary statement should be included regarding the moderate favorable evidence for MDMA-assisted therapy for PTSD.	*Thank you for this comment. As stated above, we reassessed our Strength of Evidence (SOE) rating for MDMA-assisted psychotherapy for PTSD (now rated as low SOE) accounting for the limitations that you and other reviewers highlighted. We also provide more context regarding generalizability and emphasize that findings are preliminary.*
62	8	Minor edit needed on page 2 - I believe that "PTSD-assisted psychotherapy" should be changed to "MDMA-assisted psychotherapy for PTSD"	*Change made.*

APPENDIX E: RESEARCH IN PROGRESS

Status	Study Title	Study Design	Information Resources
Clinical Trials			
Substance Use Disorder			
Not yet recruiting	Safety and Feasibility of Psilocybin in Methamphetamine Use Disorder in a Community-Based Sample	Pre-post study	ClinicalTrials.gov Identifier: NCT05322954
Not yet recruiting	A Randomized, Double-Blind Study of Psilocybin for Opioid Use Disorder in Patients on Methadone Maintenance with Ongoing Opioid Use	Crossover RCT	ClinicalTrials.gov Identifier: NCT05242029
Not yet recruiting	Psilocybin-Enhanced Psychotherapy for Methamphetamine Use Disorder	RCT	ClinicalTrials.gov Identifier: NCT04982796
Not yet recruiting	Psilocybin for Treatment of Alcohol Use Disorder: a Feasibility Study	Pre-post study	ClinicalTrials.gov Identifier: NCT04718792
Active, not recruiting	Pilot Trial of Visual Healing®, a Nature-themed Virtual Immersive Experience, to Optimize Set and Setting in Psilocybin-assisted Therapy for Alcohol Use Disorder	RCT	ClinicalTrials.gov Identifier: NCT04410913
Recruiting	Phase I Study of the Safety and Adjunctive Effects of Psilocybin in Adults with Opioid Use Disorder Maintained on Buprenorphine/Naloxone	Pre-post study	ClinicalTrials.gov Identifier: NCT04161066
Unknown	Open-Label Proof of Concept Feasibility Study to Explore the Safety, Tolerability and Potential Role of MDMA-Assisted Psychotherapy for the Treatment of Detoxified Patients with Alcohol Use Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT04158778
Recruiting	Phase II, Randomized, Double Blind, Placebo Controlled, Parallel Group, Single Center Study of Psilocybin Efficacy and Mechanism in Alcohol Use Disorder	RCT	ClinicalTrials.gov Identifier: NCT04141501
Recruiting	Preliminary Efficacy and Safety of Ibogaine in the Treatment of Methadone	RCT	ClinicalTrials.gov Identifier: NCT04003948
Not yet recruiting	Tolerability and Efficacy of Ibogaine in the Treatment of Alcoholism: The First Randomized, Double-blind, Placebo-controlled, Escalating-dose, Phase 2 Trial	RCT	ClinicalTrials.gov Identifier: NCT03380728
Recruiting	Psilocybin-facilitated Treatment for Cocaine Use: A Pilot Study	RCT	ClinicalTrials.gov Identifier: NCT02037126
Recruiting	Psilocybin-facilitated Smoking Cessation Treatment: A Pilot Study	RCT	ClinicalTrials.gov Identifier: NCT01943994

Status	Study Title	Study Design	Information Resources
Unknown	Effects and Therapeutic Potential of Psilocybin in Alcohol Dependence	Pre-post study	ClinicalTrials.gov Identifier: NCT01534494
Recruiting	Ibogaine to Determine Maximum Tolerated Dose (MTD) or Treat-to-Target Dose (TTD) for the Evaluation of Efficacy and Safety	RCT	ClinicalTrials.gov Identifier: NCT05029401
Anxiety Disorders			
Not yet recruiting	Effects of Repeated Dosing of Psilocybin on Obsessive-Compulsive Disorder: A Randomized, Waitlist-Controlled Study	RCT	ClinicalTrials.gov Identifier: NCT05370911
Recruiting	Social Anxiety MDMA-Assisted Therapy Investigation (SAMATI): A Randomized, Delayed Treatment Control Phase 2 Study of the Safety and Effectiveness of Manualized MDMA-Assisted Therapy for the Treatment of Social Anxiety Disorder	RCT	ClinicalTrials.gov Identifier: NCT05138068
Not yet recruiting	Open Label, Phase 1 Study for Evaluating the Feasibility, Safety and Efficacy of Psychotherapy Assisted Psilocybin for Treatment of Severe OCD	Pre-post study	ClinicalTrials.gov Identifier: NCT04882839
Recruiting	Psilocybin Treatment in Obsessive-Compulsive Disorder: a Preliminary Efficacy Study and Exploratory Investigation of Neural Correlates.	RCT	ClinicalTrials.gov Identifier: NCT03356483
Completed	LSD Treatment in Persons Suffering from Anxiety Symptoms in Severe Somatic Diseases or in Psychiatric Anxiety Disorders: a Randomized, Double-blind, Placebo-controlled Phase II Study	Crossover RCT	ClinicalTrials.gov Identifier: NCT03153579
Mood Disorders			
Not yet recruiting	An Open Label Study of Single-Dose Psilocybin for Major Depressive Disorder with Co-occurring Borderline Personality Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT05399498
Not yet recruiting	A Phase I/IIa, Randomized, Double-Blind, Placebo-Controlled Study to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Ascending Oral Doses of CYB003 in Participants with Major Depressive Disorder	RCT	ClinicalTrials.gov Identifier: NCT05385783
Recruiting	Psilocybin Versus Ketamine - Fast Acting Antidepressant Strategies in Treatment-resistant Depression	RCT	ClinicalTrials.gov Identifier: NCT05383313
Not yet recruiting	The Effects of Psilocybin on Self-Focus and Self-Related Processing in Treatment Resistant MDD	Pre-post study	ClinicalTrials.gov Identifier: NCT05381974
Not yet recruiting	Microdosing Psychedelics to Improve Mood	Crossover RCT	ClinicalTrials.gov Identifier: NCT05259943
Not yet recruiting	Psilocybin-assisted Cognitive Behavioral Therapy for Depression	Pre-post study	ClinicalTrials.gov Identifier: NCT05227612

Status	Study Title	Study Design	Information Resources
Recruiting	An Open-Label Pilot Study Examining the Feasibility, Safety, and Effectiveness of Psilocybin Therapy for Depression in Bipolar II Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT05065294
Active, not recruiting	The Efficacy and Tolerability of Psilocybin in Participants With Treatment-Resistant Depression: a Phase 2, Randomized Feasibility Study	RCT	ClinicalTrials.gov Identifier: NCT05029466
Not yet recruiting	Randomized Double Blind Placebo Controlled Assessing the Efficacy of Micro-dosed Psilocybin in Reducing Anxiety and or Depression Levels in Adults	RCT	ClinicalTrials.gov Identifier: NCT04989972
Completed	The Safety and Efficacy Of Psilocybin as an Adjunctive Therapy in Participants With Treatment Resistant Depression	Pre-post study	ClinicalTrials.gov Identifier: NCT04739865
Active, not recruiting	Fixed Order, Open-Label, Dose-Escalation Study of DMT in Humans	Non-randomized crossover trial	ClinicalTrials.gov Identifier: NCT04711915
Completed	A Phase 1/2 Study of GH001 in Patients With Treatment-Resistant Depression	Non-randomized sequential trial	ClinicalTrials.gov Identifier: NCT04698603
Recruiting	A Double-blind, Randomised, Placebo-controlled Study of Intravenous Doses of SPL026 (DMT Fumarate), a Serotonergic Psychedelic, in Healthy Subjects (Part A) and Patients With Major Depressive Disorder (Part B)	RCT	ClinicalTrials.gov Identifier: NCT04673383
Recruiting	A Phase II Randomized, Double-blind, Active Placebo-controlled Parallel Group Trial to Examine the Efficacy and Safety of Psilocybin in Treatment-resistant Major Depression	RCT	ClinicalTrials.gov Identifier: NCT04670081
Recruiting	The Effect of Psilocybin on MDD Symptom Severity and Synaptic Density - A Single Dose Randomized, Double Blind, Placebo- Controlled Phase 2 Positron Emission Tomography Study	RCT	ClinicalTrials.gov Identifier: NCT04630964
Recruiting	Psilocybin Treatment of Major Depressive Disorder With Co-occurring Alcohol Use Disorder	RCT	ClinicalTrials.gov Identifier: NCT04620759
Recruiting	Multicentre Study To Assess Safety And Efficacy Of Psilocybin In Patients With Treatment-Resistant Depression Following Completion Of COMP 001 And COMP 003 Trials (P-TRD LTFU)	Prospective cohort	ClinicalTrials.gov Identifier: NCT04519957
Recruiting	An Open Label Study of the Safety and Efficacy of Psilocybin in Participants With Treatment-Resistant Depression (P-TRD)	Pre-post study	ClinicalTrials.gov Identifier: NCT04433858
Recruiting	The Safety and Efficacy of Psilocybin in Participants With Type 2 Bipolar Disorder (BP-II) Depression	Pre-post study	ClinicalTrials.gov Identifier: NCT04433845
Enrolling by invitation	A Two-Year Observational Follow-up Study of Subjects With Major Depressive Disorder Following	Cohort (long-term follow-up)	ClinicalTrials.gov Identifier: NCT04353921

Status	Study Title	Study Design	Information Resources
	a Randomized, Double-Blind Single-Dose of Psilocybin or Niacin-Control		
Active, not recruiting	LSD Therapy for Persons Suffering From Major Depression: A Randomised, Double-blind, Active-placebo Controlled Phase II Study	RCT	ClinicalTrials.gov Identifier: NCT03866252
Completed	The Safety and Efficacy of Psilocybin in Participants With Treatment Resistant Depression	RCT	ClinicalTrials.gov Identifier: NCT03775200
Completed	Phase II, Randomized, Double Blind, Placebo Controlled, Parallel Group, Single Center Study of Psilocybin Efficacy in Major Depression	RCT	ClinicalTrials.gov Identifier: NCT03715127
Active, not recruiting	Psilocybin - Induced Neuroplasticity in the Treatment of Major Depressive Disorder	Crossover RCT	ClinicalTrials.gov Identifier: NCT03554174
Unknown	Psilocybin and Depression - Assessing the Long-term Effects of a Single Administration of Psilocybin on the Psychiatric Symptoms and Brain Activity of Patients With Severe Depression	RCT	ClinicalTrials.gov Identifier: NCT03380442
PTSD			
Recruiting	The Safety and Tolerability of COMP360 in Participants With Post-traumatic Stress Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT05312151
Recruiting	Sustaining Remission From Posttraumatic Stress Disorder (PTSD) Using Tuned Vibroacoustic Stimulation (TVS) Following MDMA-Assisted Psychotherapy	Pre-post study	ClinicalTrials.gov Identifier: NCT05274230
Not yet recruiting	Investigating the Therapeutic Effects of Psilocybin in Treatment-Resistant Post-Traumatic	Pre-post study	ClinicalTrials.gov Identifier: NCT05243329
Not yet recruiting	MDMA-Assisted Therapy for Postpartum People With Opioid Use Disorder and Coexisting Post Traumatic Stress Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT05219175
Not yet recruiting	An Open-Label Feasibility and Safety Study of MDMA-Assisted Group Therapy for the Treatment of Posttraumatic Stress Disorder in Veterans	Pre-post study	ClinicalTrials.gov Identifier: NCT05173831
Suspended	A Phase 2 Open-Label Treatment Development Study of MDMA-Assisted Cognitive Processing Therapy (CPT) for Posttraumatic Stress Disorder (PTSD)	Pre-post study	ClinicalTrials.gov Identifier: NCT05067244
Enrolling by Invitation	Long-Term Safety and Persistence of Effectiveness of Manualized MDMA-Assisted Therapy for the Treatment of Posttraumatic Stress Disorder	Retrospective cohort	ClinicalTrials.gov Identifier: NCT05066282
Withdrawn	A Phase 2, Open Label Study of the Safety and Effectiveness of MDMA-assisted Therapy for Participants With Posttraumatic Stress Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT04968938

Status	Study Title	Study Design	Information Resources
Recruiting	A Phase 2, Open-Label, Randomized Comparative Effectiveness Study for MDMA-Assisted Psychotherapy in U.S. Veterans With Chronic PTSD	RCT	ClinicalTrials.gov Identifier: NCT04784143
Enrolling by invitation	A Multi-Site Open-Label Safety Extension Study of Manualized MDMA-Assisted Psychotherapy for the Treatment of Participants With Posttraumatic Stress Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT04714359
Available	A Multi-site Expanded Access Program for MDMA-assisted Psychotherapy for Patients With Treatment-resistant PTSD	Expanded access protocol	ClinicalTrials.gov Identifier: NCT04438512
Recruiting	Open-label Phase 2 Study of MDMA-Assisted Psychotherapy in Veterans With Combat-Related, Refractory PTSD	Pre-post study	ClinicalTrials.gov Identifier: NCT04264026
Active, not recruiting	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 Posttraumatic Stress Disorder of Moderate or Greater Severity	RCT	ClinicalTrials.gov Identifier: NCT04077437
Recruiting	An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy With an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects With Posttraumatic Stress Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT04030169
Completed	An Open-Label, Multi-Site Phase 2 Study of the Safety and Effect of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder (Canada)	Pre-post study	ClinicalTrials.gov Identifier: NCT03485287
Completed	An Open-Label, Multi-Site Phase 2 Study of the Safety and Effect of Manualized MDMA-Assisted Therapy for the Treatment of Severe Posttraumatic Stress Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT03282123
Completed	A Phase 1/2 Open-Label Treatment Development Study of Methylenedioxymethamphetamine (MDMA)-Assisted Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads in Which 1 Member Has Chronic Posttraumatic Stress Disorder (PTSD)	Pre-post study	ClinicalTrials.gov Identifier: NCT02876172
Completed	An Open-Label Proof-of-Principle Study Testing the Use of an Additional MDMA-Assisted Therapy Session in People Who Relapsed After Participating in a Phase 2 Clinical Trial of MDMA-Assisted Therapy to Treat Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)	Pre-post study	ClinicalTrials.gov Identifier: NCT01458327
Terminated	MDMA-assisted Therapy in Twelve People With War and Terrorism-related Posttraumatic Stress Disorder (PTSD)	RCT	ClinicalTrials.gov Identifier: NCT00402298

Status	Study Title	Study Design	Information Resources
Eating Disorders			
Recruiting	A Phase 2a Safety and Feasibility Study Evaluating Psilocybin (TRP-8802) Administration in Concert With Psychotherapy in the Treatment of Binge Eating Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT05035927
Active, not recruiting	Evaluation of Psilocybin in Anorexia Nervosa: Safety and Efficacy	Pre-post study	ClinicalTrials.gov Identifier: NCT04661514
Active, not recruiting	Safety and Efficacy of Psilocybin for Body Dysmorphic Disorder	Pre-post study	ClinicalTrials.gov Identifier: NCT04656301
Not yet recruiting	An Open-Label, Multi-Site Phase 2 Study of the Safety and Feasibility of MDMA-Assisted Psychotherapy for Eating Disorders	Non-randomized controlled trial	ClinicalTrials.gov Identifier: NCT04454684
Recruiting	Effects of Psilocybin in Anorexia Nervosa	Pre-post study	ClinicalTrials.gov Identifier: NCT04052568
Other			
Recruiting	Safety and Efficacy of Repeated Low Dose MM-120 as Treatment for Attention Deficit Disorder (ADHD) in Adults: a Multi-center, Randomized, Double-blind, Placebo-controlled Phase 2a Proof of Concept Trial	RCT	ClinicalTrials.gov Identifier: NCT05200936
Recruiting	The Safety and Efficacy of Psilocybin in Patients With Treatment-resistant Depression and Chronic Suicidal Ideation	Pre-post study	ClinicalTrials.gov Identifier: NCT05220410

Notes. MM-120 is a form of LSD. SPL026 is also known as DMT Fumarate.
Abbreviations. ADHD=attention-deficit/hyperactivity disorder; BP-II=bipolar disorder II; CPT=cognitive processing therapy; DMT=5-methoxy-N,N-dimethyltryptamine; fMRI=functional magnetic resonance imaging; GH001=5 methoxy N,N dimethyltryptamine; LSD=lysergic acid diethylamide; LTFU=long-term follow up; MDD=major depressive disorder; MDMA=3,4-methylenedioxy-methamphetamine; MTD=maximum tolerated dose; OCD=obsessive compulsive disorder; RCT=randomized controlled trial; SAMATI=social anxiety MDMA-assisted therapy investigation; TRD=treatment resistant depression; TTD=treat-to-target dose; TVS=tuned vibroacoustic stimulation.
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