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CADTH Reference List

Psychedelic-Assisted Psychotherapy for Various Mental Health Disorders or Acquired Brain Injuries

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CADTH

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Key Messages

- Two systematic reviews, 7 randomized controlled trials, and 1 non-randomized study were identified regarding the clinical effectiveness of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries.
- One economic evaluation was identified regarding the cost-effectiveness of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries.
- No evidence-based guidelines were identified regarding the use of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries.

Research Questions

1. What is the clinical effectiveness of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries?
2. What is the cost-effectiveness of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries?
3. What are the evidence-based guidelines regarding the use of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, PsycInfo, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were psychedelics and psychotherapy. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, randomized or non-randomized studies, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2017 and January 26, 2022. Internet links were provided, where available.

Selection Criteria

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed. Open access full-text versions of evidence-based guidelines were reviewed when available.

Table 1: Selection Criteria

Criteria	Description
Population	Adults with post-traumatic stress disorder, anxiety disorders, mood disorders (e.g., depression), substance use disorders, obsessive compulsive disorders, eating disorders (any type), or acquired brain injuries (any cause)
Intervention	Psychedelic-assisted psychotherapy (i.e., the use of ketamine, esketamine, psilocybin, or MDMA in deliberate combination with any form of individual or group psychotherapy [also known as talk therapy])
Comparator	Q1 and Q2: Individual or group psychotherapy without the use of psychedelics Q3: Not applicable
Outcomes	Q1: Clinical benefits (e.g., resolution and/or reduction of post-traumatic stress disorder, anxiety, or mood disorder symptoms; quality of life; improvement in dysfunction or impairment; reduction in substance use) and harms (e.g., hypertension, tachycardia, toxicity, addiction, confusion, withdrawal symptoms, sleep problems, psychosis, hallucinogen persisting perceptive disorder, memory impairments, short-term depression) Q2: Cost-effectiveness (e.g., cost per quality-adjusted life-year gained, cost per adverse event avoided) Q3: Recommendations for best practice (e.g., dosage, contraindications, duration of treatment, how many administrations, method of administering)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, economic evaluations, evidence-based guidelines

MDMA = 3,4-methylenodioxymetamphetamine.

Results

Two systematic reviews,[1,2] 7 randomized controlled trials,[3-9] and 1 non-randomized study[10] were identified regarding the clinical effectiveness of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries. One economic evaluation was identified regarding the cost-effectiveness of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries.[11] No evidence-based guidelines were identified regarding the use of psychedelic-assisted psychotherapy in the treatment of various mental health disorders or acquired brain injuries. No relevant health technology assessments were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

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References

Health Technology Assessments

No literature identified.

Systematic Reviews

1. Illingworth BJ, Lewis DJ, Lambarth AT, et al. A comparison of MDMA-assisted psychotherapy to non-assisted psychotherapy in treatment-resistant PTSD: A systematic review and meta-analysis. *J Psychopharmacol*. 2021 May;35(5):501-511. PubMed

2. Smith KW, Sicignano DJ, Hernandez AV, White CM. MDMA-assisted psychotherapy for treatment of posttraumatic stress disorder: A systematic review with meta-analysis. *J Clin Pharmacol*. 2021 Oct 28. PubMed

Randomized Controlled Trials

3. Grabski M, McAndrew A, Lawn W, et al. Adjunctive ketamine with relapse prevention-based psychological therapy in the treatment of alcohol use disorder. *Am J Psychiatry*. 2022 Feb;179(2):152-162. PubMed

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

5. Ponte L, Jerome L, Hamilton S, et al. Sleep quality improvements after MDMA-assisted psychotherapy for the treatment of posttraumatic stress disorder. *J Trauma Stress*. 2021 Aug;34(4):851-863. PubMed

6. Dakwar E, Levin F, Hart CL, et al. A single ketamine infusion combined with motivational enhancement therapy for alcohol use disorder: A randomized midazolam-controlled pilot trial. *Am J Psychiatry*. 2020 Feb 1;177(2):125-133. PubMed

7. Wolfson PE, Andries J, Feduccia AA, et al. MDMA-assisted psychotherapy for treatment of anxiety and other psychological distress related to life-threatening illnesses: A randomized pilot study. *Sci Rep*. 2020 Nov 24;10(1):20442. PubMed

8. Dakwar E, Nunes EV, Hart CL, et al. A single ketamine infusion combined with mindfulness-based behavioral modification to treat cocaine dependence: A randomized clinical trial. *Am J Psychiatry*. 2019 Nov 1;176(11):923-930. PubMed

9. 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 (Berl)*. 2018 Nov;235(11):3137-3148. PubMed

Non-Randomized Studies

Secondary Analysis of Clinical Trials

10. Gorman I, Belser AB, Jerome L, et al. Posttraumatic growth after MDMA-assisted psychotherapy for posttraumatic stress disorder. *J Trauma Stress*. 2020 Apr;33(2):161-170. PubMed

Economic Evaluations

11. Marseille E, Kahn JG, Yazar-Klosinski B, Doblin R. The cost-effectiveness of MDMA-assisted psychotherapy for the treatment of chronic, treatment-resistant PTSD. *PLoS One*. 2020 Oct 14;15(10):e0239997. PubMed

Guidelines and Recommendations

No literature identified.

Appendix 1: References of Potential Interest

Previous CADTH Reports

12. Chao Y-S, Horton J. CADTH health technology review: Psychedelic-assisted psychotherapy for posttraumatic stress disorder, anxiety disorders, mood disorders, or substance use disorders. *Can J Health Technol*. 2021 Jun;1(6). https://www.cadth.ca/sites/default/files/attachments/2021-07/RC1363%20Psychedelics%20Final.pdf. Accessed 2022 Feb 2.

Systematic Reviews

Unclear Comparator

13. Andersen KAA, Carhart-Harris R, Nutt DJ, Erritzoe D. Therapeutic effects of classic serotonergic psychedelics: A systematic review of modern-era clinical studies. *Acta Psychiatr Scand*. 2021 Feb;143(2):101-118. PubMed

14. Varker T, Watson L, Gibson K, Forbes D, O'Donnell ML. Efficacy of psychoactive drugs for the treatment of posttraumatic stress disorder: A systematic review of MDMA, ketamine, LSD and psilocybin. *J Psychoactive Drugs*. 2021 Jan-Mar;53(1):85-95. PubMed

15. 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. *Prog Neuropsychopharmacol Biol Psychiatry*. 2020 Jan 10;96:109735. PubMed

Randomized Controlled Trials

Alternative Comparator — Active Control

16. Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry*. 2018 Jun;5(6):486-497. PubMed

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

Protocol

18. Philipp-Muller AE, Reshetukha T, Vazquez G, et al. Combining ketamine and internet-based cognitive behavioral therapy for the treatment of posttraumatic stress disorder: Protocol for a randomized controlled trial. *JMIR Res Protoc*. 2021 Jul 20;10(7):e30334. PubMed

19. Rucker J, Jafari H, Mantingh T, et al. Psilocybin-assisted therapy for the treatment of resistant major depressive disorder (PsiDeR): protocol for a randomised, placebo-controlled feasibility trial. *BMJ Open*. 2021 Dec 1;11(12):e056091. PubMed

Guidelines and Recommendations

Alternative Intervention — Psychedelic Use Without Psychotherapy

20. VA/DoD clinical practice guideline for the assessment and management of patients at risk for suicide. Version 2.0. Washington (DC): Department of Veterans Affairs, Department of Defense; 2019 May: https://www.healthquality.va.gov/guidelines/MH/srb/VADoDSuicideRiskFullCPGFinal5088919.pdf. Accessed 2022 Feb 2
See: Recommendation #10. p.41; Discussion, p.41

Alternative Intervention and Alternative Methodology — Psychedelic Use Without Psychotherapy, Expert Consensus

21. Kasper S, Cubala WJ, Fagiolini A, Ramos-Quiroga JA, Souery D, Young AH. Practical recommendations for the management of treatment-resistant depression with esketamine nasal spray therapy: Basic science, evidence-based knowledge and expert guidance. *World J Biol Psychiatry*. 2021 Jul;22(6):468-482. PubMed

22. Sanacora G, Frye MA, McDonald W, et al. A consensus statement on the use of ketamine in the treatment of mood disorders. *JAMA Psychiatry*. 2017;74(4):399. PubMed