McMaster University | HEALTH FORUM

Rapid Evidence Profile

Examining the use of psychedelic-assisted psychotherapy for Veterans

22 December 2023

[MHF product code: REP 57]

Context

- The Senate of Canada Subcommittee on Veterans Affairs has recently released a report entitled "The time is now: Granting equitable access to psychedelic-assisted psychotherapy."
- Within this report, the Senate subcommittee is recommending that Veterans Affairs Canada and the Department of National Defence, in collaboration with Health Canada and the Canadian Institutes of Health Research, as well as the applicable provincial and territorial authorities "immediately launch and fund a large-scale research program on psychedelic-assisted psychotherapy for treating those mental disorders and other conditions that have been identified as potentially being therapeutic targets for these types of interventions."
- The goal is to ensure that Veterans most likely to benefit from psychedelic-assisted psychotherapy are given access to treatment based on the best-available evidence.

+ Global evidence drawn upon

Evidence syntheses selected based on relevance, quality and recency of search

+ Forms of domestic evidence used (🍁 = Canadian)

Evaluation

Qualitative insights

+ Other types of information used

Jurisdictional scan (five countries: Australia, Canada, New Zealand, United Kingdom, United States)

*** Additional notable features**

Prepared in five business days using an 'all hands on deck' approach

Questions

- What is known about the use of psychedelic-assisted psychotherapy, including its safety and effectiveness, and whether these findings vary by groups and contexts including for those with psychotic disorders, disorders with risk of psychosis, dissociative disorders, suicide risk, family history of these conditions or with other risk factors related to the treatment?
- How is psychedelic-assisted psychotherapy being provided for Veterans in each of the 'Five Eyes' countries?

High-level summary of key findings

- We found 31 evidence syntheses and one protocol for an evidence synthesis that addressed the questions above, as well as five single studies with findings specific to Veterans.
- The included evidence syntheses and single studies primarily addressed health outcomes related to psilocybin-assisted psychotherapy for treatment-resistant depression and MDMA for post-traumatic stress disorder (PTSD).
- We did not identify any evidence syntheses comparing the use of different types of psychotherapy, but findings indicate that third-wave behavioural therapies (e.g., dialectical behavioural therapy, acceptance and commitment therapy, mindfulness-based cognitive therapy) may be appropriate, in addition to other approaches to psychotherapy identified in the evidence documents (e.g., cognitive behavioural therapy, exposure therapy, eye movement and desensitization and reprocessing therapy, non-directive supportive therapy).
- Evidence documents revealed that psychedelic-assisted psychotherapy is typically provided in three stages:

    - preparatory stage in which individuals are assessed for eligibility (i.e., ensuring diagnostic criteria are met for the condition) and participate in non-psychedelic psychotherapy sessions
    - treatment stage in which individuals are provided with the psychedelic and participate in a six- to 10-hour long psychotherapy session with two psychotherapists and another medical provider present
    - integrative stage in which participants receive additional non-psychedelic psychotherapy to reconcile insights from the experimental treatment with ongoing thoughts and behaviours.
- Included evidence documents revealed positive health outcomes from the use of ayahuasca-assisted therapy for treatment-resistant depression, ketamine-assisted psychotherapy for treatment-resistant and major depression, MDMA-assisted psychotherapy for PTSD and psilocybin-assisted therapy for depression.
- However, despite the large number of evidence syntheses found, many of these findings are based on a small number of single studies, often involving relatively few participants.
- Additional studies are needed to examine the effects of psychedelic-assisted psychotherapy on sub-populations.

Framework to organize what we looked for

- Type of psychedelic drugs used as part of psychotherapy (1)
    - Ayahuasca brew
    - Ibogaine
    - Ketamine
    - LSD
    - MDMA
    - Mescaline
    - Psilocybin
- Types of mental-health conditions
    - Anxiety
    - Depression
    - Post-traumatic stress disorder
    - Other

Box 1: Approach and supporting materials

At the beginning of each rapid evidence profile and throughout its development, we engage a subject matter expert who helps us to scope the question and ensure relevant context is taken into account in the summary of the evidence.

We identified evidence addressing the question by searching Cochrane Library and Health Systems Evidence for evidence syntheses and cost-effectiveness studies, PubMed and PsychInfo for single studies, as well as BIGG, CMA Joule and the International Guidelines Database for guidelines. We use forward or back citation searches with relevant articles to identify additional literature. All searches were conducted on 22 November 2023. We identified jurisdictional experiences by hand searching government and stakeholder websites for information relevant to the question from each of the 'Five Eyes' countries (Australia, Canada, New Zealand, U.K. and the U.S.). The search strategies used, including which websites were searched for the jurisdictional scan, are included in Appendix 1.

In contrast to synthesis methods that provide an in-depth understanding of the evidence, this profile focuses on providing an overview and key insights from relevant documents.

We searched for full evidence syntheses (or synthesis-derived products such as overviews of evidence syntheses), protocols for evidence syntheses and clinical guidelines.

We appraised the methodological quality of evidence syntheses that were deemed to be highly relevant using AMSTAR. AMSTAR rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. The AMSTAR tool was developed to assess reviews focused on clinical interventions, so not all criteria apply to evidence syntheses pertaining to delivery, financial or governance arrangements within health systems or to broader social systems. Guidelines that included a GRADE profile were prioritized for inclusion and data extraction.

A separate appendix document includes:
1) methodological details (Appendix 1)
2) summary table of the key findings from evidence syntheses and single studies (Appendix 2)
3) details about each identified synthesis (Appendix 3)
4) details about each single study (Appendix 4)
5) details from jurisdictional scan (Appendix 5)
6) documents that were excluded in the final stages of review (Appendix 6).

- Types of psychotherapy
  - Cognitive behavioural therapy
  - Dialectical behaviour therapy
  - Integrative therapy
  - Interpersonal therapy
  - Motivational enhancement therapy
  - Psychodynamic therapy
  - Solution-focused therapy
  - Psychotherapy (general)
  - Other (e.g., acceptance and commitment therapy, eye movement desensitization and reprocessing)
- System features used to get treatment to those who need it
  - Delivery arrangements (how care is organized to get the treatment to people who need it)
    - Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)
    - Who is providing/prescribing psychedelic-assisted psychotherapy
    - Where psychedelic-assistance psychotherapy is provided
    - With what supports is psychedelic-assisted therapy provided
  - Financial arrangements (how money flows to and through the system for providing the treatment, including pay-for-evidence approaches)
  - Governance arrangements (who gets to make what decisions about the treatment; including the regulatory framework(s) in which it is provided)
- Priority conditions that may face safety concerns
  - Psychotic disorders
  - Disorders with risk of psychosis
  - Dissociative disorders
  - Suicide risk
  - Family history of the above conditions
  - Those with other risk factors related to the treatment
- Priority populations
  - Veterans (in general and/or in relation to any or all of the groups below)
  - People with mental-health issues
  - People with substance-use issues
  - 2SLGBTQ+
  - Indigenous peoples
  - Women
  - People who live in rural and/or remote areas
  - People who are homeless or precariously housed
- Outcomes
  - Health outcomes
    - Mental-health outcomes
    - Safety (adverse events)
  - Care experiences
  - Provider experiences
  - Per-capita cost

What we found

We found 31 evidence syntheses and one protocol for an evidence synthesis that addressed the questions above as well as five single studies with findings specific to Veterans.

Coverage by and gaps in existing evidence syntheses

The included evidence syntheses and single studies primarily addressed psilocybin-assisted psychotherapy for treatment-resistant depression and MDMA for post-traumatic stress disorder (PTSD). However, findings for other types of psychedelic-assisted psychotherapy were also identified such as ketamine-assisted psychotherapy for anxiety, depression, PTSD and alcohol-use disorder as well as ibogaine and ayahuasca for treatment-resistant depression and PTSD.

The identified literature overwhelmingly focused on health outcomes (mental-health outcomes and adverse events), with relatively less examining care experiences and no identified findings on provider experiences or per-capita costs. With respect to system features, while delivery arrangements are frequently described in the literature (often in characteristics of studies tables included in evidence syntheses), we only identified three evidence syntheses evaluating delivery arrangements for psychedelic-assisted psychotherapy. One of the evidence syntheses evaluates the dose-response relationships for psilocybin-assisted psychotherapy for PTSD,(2) while another examines appropriate types of psychotherapy to be used in combination with psychedelics,(3) and the third evaluates the effects of preparation sessions prior to substance-assisted psychotherapy.(4) We did not identify any evidence documents that examined financial arrangements or governance arrangements, nor did we identify evidence documents that explicitly examined the effects on individuals with priority conditions that may face safety concerns.

The included literature examined relatively few of the priority populations included in the organizing framework, apart from individuals with mental-health conditions (which were the focus of all included documents) and Veterans (which were the explicit focus of five single studies, one of which is a Phase 2 clinical trial for psilocybin-assisted psychotherapy for PTSD that is cited in almost all included evidence syntheses).(5)

Relatively few evidence documents included equity considerations. One exception was a recent medium-quality evidence synthesis which examined the extent to which people of colour are represented in psychedelic-assisted psychotherapy trials and found approximately 82.3% of all participants are white.(6) This finding is skewed relative to the demographics in which countries are undertaken, leading to challenges generalizing findings from studies to broader populations.(6)

What existing evidence syntheses, guidelines and highly relevant single studies tell us about the use of psychedelic-assisted psychotherapy

We did not identify any guidance or evaluative studies that provided details about what type of psychotherapy should be paired with each of the psychedelics included in the rapid evidence profile. Two recent low-quality reviews found third-wave behavioural therapies including dialectical behavioural therapy, acceptance and commitment therapy and mindfulness-based cognitive therapy demonstrated theoretical similarities with the approach to psychedelic-assisted therapy, suggesting their potential for adjunctive use.(3; 7) The mostly commonly described combination was the use of MDMA and non-directive supportive psychotherapy for treating PTSD.(5; 8; 9) Other combinations of psychedelics and psychotherapy included in the literature were:

- MDMA and cognitive behavioural therapy for PTSD,(7; 10; 11) prolonged exposure therapy for PTSD,(7; 10) eye movement desensitization and reprocessing for PTSD,(10; 11) or group therapy for PTSD (10)
- psilocybin and cognitive behavioural therapy for depression,(7; 12) motivational enhancement therapy for depression and anxiety,(12) acceptance and commitment therapy for depression,(7) music therapy,(12) non-directive supportive psychotherapy for PTSD (2)
- ketamine and prolonged exposure therapy for PTSD,(13; 14) cognitive behavioural therapy for treatment-resistant depression,(15) and mindfulness-based extinction and reconsolidation therapy for PTSD.(16)

With respect to system features, we did not identify any guidance for how to organize and deliver psychedelic-assisted psychotherapy. The development of standard protocols for these services was called for in some evidence syntheses.(13; 17; 18)

The included evidence documents described psychedelic-assisted psychotherapy as being delivered in three stages: preparation, experimental treatment and integration.(7) The preparation stage included screening patients for eligibility (i.e., that specific diagnostic criteria were met) and establishing a therapeutic relationship over the course of between three and 12 preparatory sessions of non-psychedelic assisted psychotherapy.(10; 16; 19-21) One recent medium-quality evidence synthesis focused on safety considerations for the use of psychedelic-assisted psychotherapies and highlighted the importance of extensive preparation.(4) The evidence synthesis described that screening participants should include a detailed medical history (including any medications that are currently being used), blood chemistry profile, urinalysis and, if applicable, a pregnancy test. The evidence synthesis described the importance of ensuring that the treatment is provided in a comfortable setting in which the individual feels safe and that preparation sessions should take place in the same facilities as the experimental sessions.(4) The evidence synthesis found that effective preparation reduced resistance to psychedelic therapies, enhanced therapeutic effects and reduced the occurrence of adverse events.(4)

Evidence syntheses and primary studies reported between one and three experimental sessions where the psychedelics were administered. These sessions often include a co-therapist team to help avoid exhaustion as they last between six and 10 hours.(8; 9; 19-22) Additional supports provided during the experimental treatment stage include an additional medical professional (often a nurse) to monitor vital signs and to provide medical care in the case of an adverse event as well as the use of music and bodywork techniques (e.g., breathwork, body scanning, meditation) which can enhance the therapeutic experience.(12) Additional considerations are needed for the administration of ketamine, which is often provided intravenously and requires a more clinical setting and the presence of an anesthesiologist.(13) The exception to this is the use of esketamine for treatment-resistant depression, which is taken as a nasal spray.

The final stage is integration sessions, in which non-psychedelic-assisted psychotherapy is provided in efforts to reconcile insights achieved during the experimental treatment with ongoing thoughts and behaviours. Evidence documents reported between three and eight integration sessions, but no evaluation of the optimal number of sessions were identified.(7; 12; 21)

As mentioned above, no evidence documents were identified that addressed either financial or governance arrangements.

What existing syntheses, guidelines and highly relevant single studies tell us about the effects on equity-centred quadruple-aim metrics

Included evidence documents addressed two of the four equity-centred quadruple-aim metrics – health outcomes and to a lesser extent care experiences. We did not identify any evidence documents that included findings relevant to either provider experiences or per-capita costs. Below, we synthesize the included evidence by type of psychedelic with additional insights available in Appendix 2, 3 and 4.

Ayahuasca

One recent high-quality evidence synthesis and one recent medium-quality evidence synthesis found improvements in symptoms of treatment-resistant depression from ayahuasca-assisted psychotherapy (23; 24)

Ibogaine

Two studies provided insights into ibogaine for treatment-resistant depression and PTSD, both examining its use among U.S. Special Operations Forces Veterans.(25; 26) The studies reported improvements in self-reported depression symptoms and self-reported PTSD symptoms.(25; 26) Younger Veterans and those with higher baseline depression scores reported larger symptom improvements.(26)

Ketamine

One older high-quality evidence synthesis and four recent medium-quality evidence syntheses found improvements in treatment-resistant depression and major depression following ketamine-assisted psychotherapy.(13; 17; 27-29) One study included in a recent medium-quality evidence synthesis found sustained improvements in depression scores, and a longer time until depression relapse from ketamine-assisted cognitive behavioural therapy compared to ketamine alone.(15)

Two medium-quality evidence syntheses reported some improvements in substance use, particularly for alcohol-use disorder, following ketamine-assisted psychotherapy.(17; 27)

One older high-quality review found no evidence for the effects of ketamine in treating anxiety and rated the evidence for ketamine treating PTSD as being 'unknown' due to inclusion of relatively few studies.(29) Similar findings were identified in two recent medium-quality evidence syntheses, with most included studies noting no significant effect compared to psychotherapy alone but one study reported a longer treatment effect in the ketamine group.(16; 17)

LSD

We did not identify much literature related to LSD, which may be a result of looking at more recent evidence syntheses and single studies that have tended to focus on MDMA and psilocybin given recent changes in the regulatory landscape for these treatments (see description below of experiences in Australia and the U.S.). We did identify one medium-quality evidence synthesis that identified no relevant studies on LSD-assisted psychotherapy for PTSD.(16)

MDMA

Fourteen evidence syntheses reported reductions in PTSD symptoms with relatively few adverse events from MDMA-assisted psychotherapy.(7-11; 15; 16; 19; 20; 30-32) However, many of these syntheses cite the same single studies with a particular focus on a pooled analysis of six Phase 2 randomized clinical trials from the U.S.(33) One of these clinical trials is focused specifically on MDMA-assisted psychotherapy provided to Veterans and first responders with PTSD.(5) The pooled analysis found MDMA-assisted psychotherapy to be superior to both active and inactive placebo-assisted therapy in reducing PTSD symptoms.(33)

With respect to adverse events, mixed effects were reported for the interaction between MDMA and monoamine reuptake inhibitors (including SSRIs). One recent low-quality evidence synthesis noted they may reduce the effectiveness of MDMA-assisted psychotherapy, while a recent medium-quality evidence synthesis reported that this finding was not replicated in later studies.(4; 34) One recent low-quality evidence synthesis found adverse events reported in MDMA-assisted psychotherapy included anxiety, jaw clenching, reduced appetite, dizziness, nausea, depressed mood, irritability and panic attacks.(19) The synthesis found events occurred more frequently with high doses of MDMA.(19)

Mescaline

We did not identify any evidence syntheses or single studies that reported on quadruple-aim outcomes of mescaline-assisted psychotherapy.

Psilocybin

One medium-quality review found significant improvements in anxiety symptoms following adjuvant psychotherapy with psilocybin.(8)

Seven recent medium-quality evidence syntheses and two recent low-quality evidence syntheses found significant improvements in depression symptoms (including for treatment-resistant depression) following psychotherapy with psilocybin with few adverse reactions.(2; 7; 8; 12; 15; 22; 24; 35; 36) One recent medium-quality evidence synthesis found that treatment-resistant depression responds best to higher doses of psilocybin (40 mg/70 kg), but patients with co-morbid anxiety and depression respond better to lower doses (10–25 mg/70kg).(2) Adverse events reported during psilocybin-assisted psychotherapy included elevated blood pressure, physical discomfort, transient mild to moderate headache, nausea and feelings of panic.(2) The likelihood of these events increased with higher dosages but remained relatively rare and were predominantly dealt with during treatment by present healthcare providers.(2)

Finally, one study included in a recent medium-quality evidence synthesis found positive outcomes on smoking cessation for the use of psilocybin and cognitive behavioural therapy.(15)

Care experiences

Participants in one study included in a recent medium-quality evidence synthesis reported gaining novel insights into themselves and their presenting problems following psilocybin-assisted psychotherapy.(12)

Veterans participating in a single study reported seeking access to psilocybin after experiencing barriers accessing other PTSD treatments and described their experience as being associated with changes in their perception and learning.(37)

Experiences from Five Eyes countries (including all provinces and territories in Canada)

For the jurisdictional scan, we looked at the federal level in each of the 'Five Eyes' countries – Australia, Canada, New Zealand, U.K. and U.S. – for psychedelic-assisted psychotherapy services for Veterans. We were unable to find any information related to psychedelic-assisted psychotherapy in New Zealand.

We were unable to identify any programs run by national Veterans Affairs departments (or offices) that provide psychedelic-assisted therapy services. However, as recently as 1 July 2023, psychiatrists in Australia can prescribe MDMA and psilocybin for controlled clinical use including in the treatment of PTSD and treatment-resistant depression. Access to these drugs requires pre-approval via the Therapeutic Goods Administration and must be taken in a controlled setting in combination with psychotherapy (though the type of psychotherapy is not specific). There is currently no coverage for these services under the Medicare benefits schedule and we could not identify any financial coverage specific to Veterans. Similarly, in Canada, an amendment was made in 2021 to the special access program permitting requests for psilocybin and MDMA by an individual's physician (or in some provinces and territories another provider with prescribing privileges) to treat "serious and life-threatening conditions where conventional treatments have failed, are unsuitable or are not available in Canada." If approved, psychedelic-assisted therapy must be provided by a professional with previous experience delivering this type of care and providers must maintain credible records including the quantity of the drug received and any adverse reactions.

Apart from these broader changes, Veterans in the 'Five Eyes' countries may access psychedelic-assisted psychotherapy through two pathways. The first is through charitable organizations that operate in the U.S. and the U.K. that provide resources and grants (as well as preparation and integration coaching) for Veterans to travel to other countries to access psychedelic-assisted therapy in countries where the consumption and procurement of some psychedelics is legal (i.e., Jamaica, Mexico, Peru). Examples of these include VETS and the Heroic Hearts Project (which has both a U.S. and U.K. chapter).

The second pathway, if eligible, is participation in a clinical trial. In each of Australia, Canada, U.K. and the U.S. we identified ongoing clinical trials for Veterans. In the U.S., the Food and Drug Administration granted breakthrough therapy designation to MDMA and psilocybin to expedite their development and review to treat mental-health conditions, given preliminary evidence indicates they offer substantial improvement over other available therapies. The Department of Veterans Affairs in the U.S. is currently funding clinical trials on the effectiveness of MDMA

and psilocybin as treatment for PTSD. Similarly, in Canada, the federal government recently invested $3 million CAD in three clinical trials on the use of psilocybin assisted psychotherapy, one of which related to treatment-resistant depression may be relevant to Veterans.

Ketamine differs compared to the other psychedelics examined in this rapid evidence profile as in 'Five Eyes' countries it is categorized as a controlled substance, given its use as an anaesthetic. In the U.K., though not specific to Veterans, the Medicine and Healthcare products Regulatory Agency fast-tracked the designation of ketamine-assisted psychotherapy for the treatment of severe alcohol-use disorder. However, despite some early supportive evidence, its use in the form of a nasal spray has not been recommended by the National Institute for Health and Care Excellence for treatment-resistant depression.

Waddell K, Velez M, DeMaio P, Jaspal A, Wilson MG. Rapid evidence profile 57: Examining the use of psychedelic-assisted psychotherapy for Veterans. Hamilton: McMaster Health Forum, 22 December 2023.

This rapid evidence profile was funded by the Chronic Pain Centre of Excellence for Canadian Veterans and the Atlas Institute for Veterans and Families, which in turn are funded by Veterans Affairs Canada. The McMaster Health Forum receives both financial and in-kind support from McMaster University. The views expressed in the rapid evidence profile are the views of the authors and should not be taken to represent the views of the Chronic Pain Centre of Excellence for Canadian Veterans, the Atlas Institute for Veterans and Families or McMaster University.

References

1. Tupper KW, Wood E, Yensen R, Johnson MW. Psychedelic medicine: A re-emerging therapeutic paradigm. *Canadian Medical Association Journal* 2015; 187(14): 1054-59.
2. Perez N, Langlest F, Mallet L, et al. Psilocybin-assisted therapy for depression: A systematic review and dose-response meta-analysis of human studies. *European Neuropsychopharmacology* 2023; 76: 61-76.
3. Walsh Z, Thiessen MS. Psychedelics and the new behaviourism: considering the integration of third-wave behaviour therapies with psychedelic-assisted therapy. *Internal Review of Psychiatry* 2018; 30(4): 343-49.
4. Thal SB, Wieberneit M, Sharbanee JM, et al. Therapeutic (Sub)stance: Current practice and therapeutic conduct in preparatory sessions in substance-assisted psychotherapy – A systematized review. *Journal of Psychopharmacoly* 2022; 36(11): 1191-1207.
5. Mithoefer MC, Mithoefer AT, Feduccia AA, et al. 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: A randomised, double-blind, dose-response, phase 2 clinical trial. *Lancet Psychiatry* 2018; 5(6): 486-97.
6. Michaels TI, Purdon J, Collins A, Williams MT. Inclusion of people of color in psychedelic-assisted psychotherapy: A review of the literature. *BMC Psychiatry* 2018; 18(1): 245.
7. Reiff CM, Richman EE, Nemeroff CB, et al. Psychedelics and psychedelic-assisted psychotherapy. *American Journal of Psychiatry* 2020; 177(5): 391-410.
8. Chao YS, Horton J. CADTH Health Technology Review. Psychedelic-assisted psychotherapy for post-traumatic stress disorder, anxiety disorders, mood disorders, or substance use disorders. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2021.
9. Morgan L. MDMA-assisted psychotherapy for people diagnosed with treatment-resistant PTSD: What it is and what it isn't. *Annals of General Psychiatry* 2020; 19: 33.
10. Hoskins MD, Sinnerton R, Nakamura A, et al. Pharmacological-assisted psychotherapy for post-traumatic stress disorder: A systematic review and meta-analysis. *European Journal of Psychotraumatology* 2021; 12(1): 1853379.
11. Riaz K, Suneel S, Hamza Bin Abdul Malik M, et al. MDMA-Based psychotherapy in treatment-resistant post-traumatic stress disorder (PTSD): A brief narrative overview of current evidence. *Diseases* 2023; 11(4).
12. Horton DM, Morrison B, Schmidt J. Systematized review of psychotherapeutic components of psilocybin-assisted psychotherapy. *American Journal of Psychotherapy* 2021; 74(4): 140-49.
13. Philipp-Muller AE, Stephenson CJ, Moghimi E, et al. Combining ketamine and psychotherapy for the treatment of posttraumatic stress disorder: A systematic review and meta-analysis. *Journal of Clinical Psychiatry* 2023; 84(2): 22br14564.
14. Shiroma PR, Thuras P, Wels J, Erbes C, Kehle-Forbes S, Polusny M. A proof-of-concept study of subanesthetic intravenous ketamine combined with prolonged exposure therapy among veterans with posttraumatic stress disorder. *Journal of Clinical Psychiatry* 2020; 81(6).
15. Wheeler S, Dyer N. A systematic review of psychedelic-assisted psychotherapy for mental health: An evaluation of the current wave of research and suggestions for the future. *Psychology of Consciousness: Theory, Research, and Practice* 2020; 7(3): 279-315.
16. 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. *Journal of Psychoactive Drugs* 2021; 53(1): 85-95.
17. Kew BM, Porter RJ, Douglas KM, Glue P, Mentzel CL, Beaglehole B. Ketamine and psychotherapy for the treatment of psychiatric disorders: systematic review. *BJPsych Open* 2023; 9(3): e79.
18. Trope A, Anderson BT, Hooker AR, Glick G, Stauffer C, Woolley JD. Psychedelic-assisted group therapy: A systematic review. *Journal of Psychoactive Drugs* 2019; 51(2): 174-88.
19. Smith KW, Sicignano DJ, Hernandez AV, White CM. MDMA-assisted psychotherapy for treatment of posttraumatic stress disorder: A systematic review with meta-analysis. *Journal of Clinical Pharmacology* 2022; 62(4): 463-71.

20. 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 Neuropsychopharmacology Biology and Psychiatry* 2020; 96: 109735.

21. Cavarra M, Falzone A, Ramaekers JG, Kuypers KPC, Mento C. Psychedelic-assisted psychotherapy – A systematic review of associated psychological interventions. *Front Psychol*ogy 2022; 13: 887255.

22. Dawood Hristova JJ, Pérez-Jover V. Psychotherapy with psilocybin for depression: Systematic review. *Behavioural Science (Basel)* 2023; 13(4): 297.

23. Mackey K, Anderson J, Williams B, Parr N. Evidence brief: Psychedelic medications for mental health and substance use disorders. Washington, DC: VA Office of Research and Development; 2022.

24. Rosenblat JD, Husain MI, Lee Y, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force report: Serotonergic psychedelic treatments for major depressive disorder. *Canadian Journal of Psychiatry* 2023; 68(1): 5-21.

25. Davis AK, Xin Y, Sepeda N, Averill LA. Open-label study of consecutive ibogaine and 5-MeO-DMT assisted-therapy for trauma-exposed male Special Operations Forces Veterans: prospective data from a clinical program in Mexico. *American Journal of Drug and Alcohol Abuse* 2023; 49(5): 587-96.

26. Xin Y, Armstrong SB, Averill LA, Sepeda N, Davis AK. Predictors of psychedelic treatment outcomes among special operations forces veterans. *Psychology of Consciousness: Theory, Research, and Practice* 2023.

27. Joneborg I, Lee Y, Di Vincenzo JD, et al. Active mechanisms of ketamine-assisted psychotherapy: A systematic review. *Journal of Affective Disordorder* 2022; 315: 105-12.

28. Drozdz SJ, Goel A, McGarr MW, et al. Ketamine assisted psychotherapy: A Systematic narrative review of the literature. *Journal of Pain Research* 2022; 15: 1691-706.

29. Varker T, Watson L, Gibson K, Knight H, O'Donnell M. Hallucinogens as treatments for PTSD, anxiety and depression: A rapid evidence assessment. Australia: Phoenix Australia Centre for Posttraumatic Mental Health; 2017.

30. Illingworth BJ, Lewis DJ, Lambarth AT, Stocking K, Duffy JM, Jelen LA, Rucker JJ. A comparison of MDMA-assisted psychotherapy to non-assisted psychotherapy in treatment-resistant PTSD: A systematic review and meta-analysis. *Jorunal of Psychopharmacology* 2021; 35(5): 501-11.

31. Szafoni S, Więckiewicz G, Pudlo R, Gorczyca P, Piegza M. Will MDMA-assisted psychotherapy become a breakthrough in treatment-resistant post-traumatic stress disorder? A critical narrative review. *Psychiatric Policy* 2022;56(4): 823-36.

32. 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): 337-44.

33. Mithoefer MC, Feduccia AA, Jerome L, et al. MDMA-assisted psychotherapy for treatment of PTSD: study design and rationale for phase 3 trials based on pooled analysis of six phase 2 randomized controlled trials. *Psychopharmacology (Berl)* 2019; 236(9): 2735-45.

34. Sarparast A, Thomas K, Malcolm B, Stauffer CS. Drug-drug interactions between psychiatric medications and MDMA or psilocybin: a systematic review. *Psychopharmacology (Berl)* 2022; 239(6): 1945-76.

35. Haikazian S, Chen-Li DCJ, Johnson DE, et al. Psilocybin-assisted therapy for depression: A systematic review and meta-analysis. *Psychiatry Res* 2023; 329: 115531.

36. Khan AJ, Bradley E, O'Donovan A, Woolley J. Psilocybin for trauma-related disorders. *Current Top Behaviour Neuroscience* 2022; 56: 319-32.

37. Smith F, Neill J, Wainwright V. An interpretative phenomenological analysis of the use of psilocybin by veterans with symptoms of trauma. *Drug Science, Policy and Law* 2022; 8: 20503245221124117.