

## Appendix 1: Methodological details

We use a standard protocol for preparing rapid evidence profiles (REP) to ensure that our approach to identifying research evidence is as systematic and transparent as possible in the time we were given to prepare the profile.

## Examining the use of psychedelic-assisted psychotherapy for Veterans

**22 December 2023**

[MHF product code: REP 57]

### Identifying research evidence

For this REP, we searched the Cochrane Library and Health Systems Evidence for evidence syntheses and protocols for evidence syntheses, BIGG, CMA Joule and the International Guidelines Database for guidelines, and PubMed and PsychInfo for evidence syntheses and single studies.

In [Cochrane](#) and [Health Systems Evidence](#), we searched for psychedelic OR MDMA OR psilocybin OR ketamine. In [BIGG](#), we searched for consumption of psychoactive substances category combined with psychotherapy in open search. In CMA Joule and International Guidelines Database, we searched for psychedelic OR MDMA OR psilocybin OR ketamine. In [PubMed](#) and PsychInfo, we searched for (psychedelic OR MDMA OR psilocybin OR ketamine) AND psychotherapy. Given the large number of results from PubMed and PsychInfo, we limited results to the past 10 years and focused on identifying evidence syntheses and single studies related to Veterans or that had been conducted in Canada. Links provide access to the full search strategy.

Each source for these documents is assigned to one team member who conducts hand searches (when a source contains a smaller number of documents) or keyword searches to identify potentially relevant documents. A final inclusion assessment is performed both by the person who did the initial screening and the lead author of the rapid evidence profile, with disagreements resolved by consensus or with the input of a third reviewer on the team. The team uses a dedicated virtual channel to discuss and iteratively refine inclusion/exclusion criteria throughout the process, which provides a running list of considerations that all members can consult during the first stages of assessment.

During this process we include published, pre-print and grey literature. We do not exclude documents based on the language of a document. However, we are not able to extract key findings from documents that are written in languages other than Chinese, English, French, Portuguese or Spanish. We provide any documents that do not have content available in these languages in an appendix containing documents excluded at the final stages of reviewing. We excluded documents that did not directly address the research questions and the relevant organizing framework.

### Assessing relevance and quality of evidence

We assess the relevance of each included evidence document as being of high, moderate or low relevance to the question.

Two reviewers independently appraised the quality of the guidelines we identified as being highly relevant using AGREE II. We used three domains in the tool (stakeholder involvement, rigour of development and editorial independence) and classified guidelines as high quality if they were scored as 60% or higher across each of these domains.

Two reviewers independently appraise the methodological quality of evidence syntheses that are deemed to be highly relevant. Disagreements are resolved by consensus with a third reviewer if needed. AMSTAR rates overall methodological quality on a scale of 0 to 11, where 11/11 represents an evidence synthesis of the highest quality. High-quality evidence syntheses are those with scores of eight or higher out of a possible 11, medium-quality evidence syntheses are those with scores between four and seven, and low-quality evidence syntheses are those with scores less than four. It is important to note that the AMSTAR tool was developed to assess evidence syntheses focused on clinical interventions, so not all criteria apply to those pertaining to health-system arrangements or to economic and social responses. Where the denominator is not 11, an aspect of the tool was considered not relevant by the raters. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, an evidence synthesis that scores 8/8 is generally of comparable quality to another scoring 11/11; both ratings are considered 'high scores.' A high score signals that readers of the evidence synthesis can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the evidence synthesis should be discarded, merely that less confidence can be placed in its findings and that the evidence synthesis needs to be examined closely to identify its limitations. (Lewin S, Oxman AD, Lavis JN, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Research Policy and Systems* 2009; 7 (Suppl1): S8.)

### **Identifying experiences from other countries and from Canadian provinces and territories**

For each REP, we work with the requestors to collectively decide on what countries (and/or states or provinces) to examine based on the question posed. For other countries, we search relevant government and stakeholder websites including the websites of Departments or Offices of Veterans Affairs as well as the websites of Veterans health insurance providers. In Canada, a similar approach was used, searching the websites of Department of National Defence and Veterans Affairs Canada as well as Medavie Blue Cross. While we do not exclude content based on language, where information is not available in English, Chinese, French, Portuguese or Spanish, we attempt to use site-specific translation functions or Google Translate. A full list of websites and organizations searched is available upon request.

### **Preparing the profile**

Each included document is cited in the reference list at the end of the REP. For all included guidelines, evidence syntheses and single studies (when included), we prepare a small number of bullet points that provide a summary of the key findings, which are used to summarize key messages in the text. Protocols and titles/questions have their titles hyperlinked, given that findings are not yet available. For this profile, we only prepared bulleted summaries of key findings for documents deemed to be of high relevance. For those classified as medium or low relevance, we list the title with a link to the primary source for easy retrieval if needed.

We then draft a summary that highlights the key findings from all highly relevant documents (alongside their date of last search and methodological quality), as well as key findings from the jurisdictional scan.

Upon completion, the REP is sent to the subject matter expert for their review.

## Appendix 2: Summary of evidence about outcomes from the use of psychedelic-assisted psychotherapy

Types of psychedelic drugs used as part of psychotherapy	Anxiety	Depression	Post-traumatic stress disorder	Other
General	No outcomes identified	No outcomes identified	<i>Care experiences</i> <ul style="list-style-type: none"> <li>One recent medium-quality evidence synthesis found effective preparation sessions to establish therapeutic rapport and provide education on substance effects reduced resistance to psychedelic-assisted therapies and improved therapeutic effects (1)</li> </ul>	No outcomes identified
Ayahuasca	No outcomes identified	<i>Health outcomes</i> <ul style="list-style-type: none"> <li>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 (2; 3)</li> </ul>	No outcomes identified	No outcomes identified
Ibogaine	No outcomes identified	<i>Health outcomes</i> <ul style="list-style-type: none"> <li>One single study reported improvements in self-reported depression symptoms following ibogaine-assisted therapy among trauma-exposed U.S. Special Operations Forces Veterans <ul style="list-style-type: none"> <li>A follow-up study found younger age and higher baseline depression were correlated with larger improvements (4)</li> </ul> </li> </ul>	<i>Health outcomes</i> <ul style="list-style-type: none"> <li>One single study found improvements in self-reported PTSD symptoms following ibogaine-assisted therapy among trauma-exposed U.S. Special Operations Forces Veterans (5)</li> </ul>	No outcomes identified
Ketamine	No outcomes identified	<i>Health outcomes</i> <ul style="list-style-type: none"> <li>Two recent medium-quality evidence syntheses found reported improvement in treatment-resistant depression following ketamine-assisted psychotherapy (6; 7)</li> <li>One older high-quality evidence-synthesis and two recent medium-quality evidence syntheses found a reduction in major depression symptoms following ketamine-assisted psychotherapy (8-10)</li> </ul>	<i>Health outcomes</i> <ul style="list-style-type: none"> <li>Two recent medium-quality evidence syntheses reported mixed effects from ketamine-assisted psychotherapy, with most included studies noting no significant effect compared to psychotherapy alone but one study reported a longer treatment effect in the ketamine group (7; 12)</li> </ul>	<i>Health outcomes</i> <ul style="list-style-type: none"> <li>Two medium-quality evidence syntheses reported some improvements in substance use following</li> </ul>

Types of psychedelic drugs used as part of psychotherapy	Anxiety	Depression	Post-traumatic stress disorder	Other
		<ul style="list-style-type: none"> <li>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 (11)</li> </ul>		ketamine-assisted (6; 7)
LSD	No outcomes identified	No outcomes identified	<i>Health outcomes</i> <ul style="list-style-type: none"> <li>A recent medium-quality evidence synthesis identified no relevant studies on LSD-assisted psychotherapy for PTSD (12)</li> </ul>	No outcomes identified
MDMA	No outcomes identified	No outcomes identified	<i>Health outcomes</i> <ul style="list-style-type: none"> <li>One recent medium-quality and two recent low-quality evidence syntheses found MDMA-assisted therapy was effective in reducing PTSD scores and PTSD symptoms to below-diagnosis threshold with relatively few adverse events (13-15)</li> <li>Two recent high-quality evidence synthesis, four recent-medium-quality evidence syntheses, two recent low-quality evidence synthesis and one older medium-quality evidence synthesis reported MDMA-assisted therapy to be superior to active and inactive placebo-assisted therapy in reducing PTSD symptoms (11; 12; 15-20)</li> <li>A recent low-quality evidence synthesis found monthly MDMA administration (for two or three months) combined with either trauma-focused cognitive therapy or eye movement desensitization reprocessing reduced PTSD symptoms (21)</li> <li>One older medium-quality evidence synthesis found MDMA-assisted psychotherapy and prolonged exposure therapy had comparable</li> </ul>	No outcomes identified

Types of psychedelic drugs used as part of psychotherapy	Anxiety	Depression	Post-traumatic stress disorder	Other
			<p>results, with a larger cumulative effect size on clinical-observed outcomes and lower percentage of patients dropping out in MDMA-assisted psychotherapy trials (22)</p> <ul style="list-style-type: none"> <li>• One Phase 2 clinical trial found active doses of MDMA with non-directive supportive psychotherapy were effective and well tolerated in reducing PTSD symptoms in Veterans and first responders (23)</li> <li>• Mixed effects of MDMA interactions with monoamine reuptake inhibitors (including SSRIs) were reported with one recent low-quality evidence synthesis noting they may reduce the effectiveness of MDMA-assisted psychotherapy, while a recent medium-quality evidence synthesis noted that this finding was not replicated in later studies (1; 24)</li> <li>• One recent low-quality evidence synthesis found adverse events reported in MDMA-assisted psychotherapy to include anxiety, jaw clenching, reduced appetite, dizziness, nausea, depressed mood, irritability and panic attacks (13) <ul style="list-style-type: none"> <li>◦ These events were more likely to occur with high doses of MDMA (13)</li> </ul> </li> </ul>	
Mescaline	No outcomes identified	No outcomes identified	No outcomes identified	No outcomes identified
Psilocybin	<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> <li>• One medium-quality evidence synthesis found significant improvements in anxiety symptoms</li> </ul>	<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> <li>• 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 adjuvant psychotherapy with psilocybin with few adverse reactions (3; 11; 15; 20; 25-29)</li> </ul>	<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> <li>• No relevant studies were identified in a recent medium-quality evidence synthesis (12)</li> </ul>	<p><i>Health outcomes</i></p> <ul style="list-style-type: none"> <li>• One study included in a recent medium-quality evidence synthesis</li> </ul>

Types of psychedelic drugs used as part of psychotherapy	Anxiety	Depression	Post-traumatic stress disorder	Other
	following adjuvant psychotherapy with psilocybin (15)	<ul style="list-style-type: none"> <li>○ Treatment-resistant depression responds best to higher doses of psilocybin, however patients with co-morbid anxiety and depression respond better to lower doses (29)</li> </ul> <p><i>Care experiences</i></p> <ul style="list-style-type: none"> <li>● Participants in one study included in a recent medium-quality evidence synthesis reported gaining novel insights into themselves and their presenting problems (25)</li> <li>● Veterans reported in one single study seeking access to psilocybin after experiencing barriers accessing PTSD treatments and described their experience as being associated with changes of perception, learning and symptoms reduction (30)</li> </ul>		found positive outcomes on smoking cessation for the use of psilocybin and cognitive behavioural therapy (11)

## Appendix 3: Key findings from evidence syntheses about the use of psychedelic-assisted psychotherapy for Veterans

Dimension of organizing framework	Declarative title and key findings	Relevance rating	Living status	Quality (AMSTAR)	Last year literature searched	Availability of GRADE profile	Equity considerations
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Psilocybin</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Anxiety</li> <li>Depression</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Cognitive behavioural therapy</li> <li>Interpersonal therapy</li> <li>Psychotherapy (general)</li> <li>Other (e.g., acceptance and commitment therapy, eye movement desensitization and reprocessing)</li> </ul> </li> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> <li>Safety (adverse events)</li> </ul> </li> <li>Care experiences</li> </ul> </li> </ul>	<p><a href="#">Research on psilocybin-assisted psychotherapy (PAP) revealed no serious adverse outcomes and showed significant improvements for depression and anxiety</a> (25)</p> <ul style="list-style-type: none"> <li>PAP was found to consist of three stages: pre-treatment sessions to prepare participants, treatment sessions where psilocybin was administered and post-treatment sessions to integrate the experience with everyday life</li> <li>Psychotherapy modalities integrated into psilocybin-assisted psychotherapy interventions include music therapy, motivational enhancement therapy (MET), cognitive behavioural therapy (CBT), supportive-expressive group therapy, eclectic psychotherapeutic intervention and various psychotherapeutic techniques such as body scanning, writing, guided imagery, integration sessions and meditation practices</li> <li>Quantitative outcomes across studies consistently showed statistically significant improvements in targeted outcomes, including large effect sizes for therapeutically relevant constructs such as depression and anxiety, with only common transient and mild adverse events reported</li> <li>Qualitative outcomes emphasized participants gaining novel insights into themselves and their presenting problems, with psychotherapeutic support, particularly through music, playing a crucial role in achieving clinically significant outcomes in PAP studies</li> </ul>	High	No	4/10	2021	No	None identified
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>MDMA</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Post-traumatic stress disorder</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Psychotherapy (general)</li> </ul> </li> <li>Delivery arrangements</li> </ul>	<p><a href="#">MDMA-assisted therapy was superior to active and inactive placebo-assisted therapy in reducing PTSD symptoms, while conventional pharmacological-assisted psychotherapies were not found to be superior to placebo</a> (16)</p> <ul style="list-style-type: none"> <li>A range of different types of therapies were used including CBT, prolonged exposure therapy (in some cases using virtual reality) and group therapy</li> <li>The number of therapy sessions in included studies differed with between 6–12 sessions of psychotherapy prior to the session where MDMA was administered</li> </ul>	High	No	6/11	2016	No	None identified

<ul style="list-style-type: none"> <li>○ Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>● Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> </ul> </li> </ul> </li> </ul>							
<ul style="list-style-type: none"> <li>● Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ MDMA</li> </ul> </li> <li>● Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Post-traumatic stress disorder</li> </ul> </li> <li>● Types of psychotherapy <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> <li>● Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> <li>▪ Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<a href="#">MDMA-assisted psychotherapy was found to be promising compared to active and inactive placebo groups for improving PTSD symptoms and demonstrated minimal physical and neurocognitive risk, but better powered randomized control trials (RCTs) are needed</a> (17) <ul style="list-style-type: none"> <li>● Certain symptomatology clusters or trauma etiologies, including combat or domestic violence, may benefit more from MDMA-assisted psychotherapy, and sub-group analyses should be undertaken to understand who is most likely to respond</li> </ul>	High	No	4/11	2020	No	None identified
<ul style="list-style-type: none"> <li>● Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Ketamine</li> </ul> </li> <li>● Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Depression</li> </ul> </li> <li>● Types of psychotherapy <ul style="list-style-type: none"> <li>○ Cognitive behavioural therapy</li> <li>○ Motivational enhancement therapy</li> <li>○ Psychotherapy (general)</li> <li>○ Other (e.g., acceptance and commitment therapy, eye movement desensitization and reprocessing)</li> </ul> </li> <li>● Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> </ul> </li> </ul> </li> </ul>	<a href="#">Ketamine-assisted psychotherapy may result in improvements in substance use but was not effective in improving treatment-resistant depression</a> (6) <ul style="list-style-type: none"> <li>● Temporary neural changes caused by ketamine, including n-methyl-D-aspartate receptor (NMDAR) inhibition and increase of synaptic neuroplasticity, appeared to affect treatment outcomes of ketamine-assisted psychotherapy (KAP), which showed significant positive effects on substance use, but found no evidence of improving treatment-resistant depression</li> <li>● The lack of large, replicated clinical trials with rigorous designs and focus on mechanisms of action limit the ability to judge the utility of KAP</li> </ul>	Medium	No	5/9	2021	No	None identified
<ul style="list-style-type: none"> <li>● Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Ketamine</li> </ul> </li> </ul>	<a href="#">The combination of ketamine and psychotherapy showed promising results for the treatment of psychiatric disorders, but study heterogeneity and the lack of large trials prevent clear recommendations</a> (7)	High	No	7/10	2022	No	None identified



<ul style="list-style-type: none"> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Anxiety</li> <li>Depression</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Cognitive behavioural therapy</li> <li>Motivational enhancement therapy</li> <li>Psychotherapy (general)</li> <li>Other (e.g., acceptance and commitment therapy, eye movement desensitization and reprocessing)</li> </ul> </li> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>Manualized psychotherapies and standardized ketamine protocols specifying sequencing of ketamine-assisted psychotherapy are necessary to inform specific recommendations for the use of ketamine to improve psychiatric disorders</li> </ul>						
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>MDMA</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Post-traumatic stress disorder</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Cognitive behavioural therapy</li> <li>Psychotherapy (general)</li> <li>Other (e.g., acceptance and commitment therapy, eye movement desensitization and reprocessing)</li> </ul> </li> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> <li>Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<p><a href="#">Monthly MDMA administration combined with psychotherapy sessions has demonstrated efficacy in reducing PTSD symptoms, with positive outcomes associated with a strong therapeutic alliance, neurohormonal influences such as oxytocin and serotonin, and the alleviation of comorbidities</a> (21)</p> <ul style="list-style-type: none"> <li>Common treatments for PTSD include trauma-focused cognitive behavioural therapy and eye movement desensitization and reprocessing (EMDR)</li> <li>MDMA-assisted therapy may also be specifically useful for people with PTSD experiencing racism</li> </ul>	High	No	2/9	2023	No	Race/ethnicity/culture/language
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Ayahuasca brew</li> <li>LSD</li> <li>Mescaline</li> <li>Psilocybin</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Depression</li> </ul> </li> </ul>	<p><a href="#">Preliminary findings suggest that psilocybin and ayahuasca were effective for treatment-resistant depression, and psilocybin combined with psychotherapy demonstrated efficacy and safety for major depressive disorder and cancer-related depression</a> (3)</p> <ul style="list-style-type: none"> <li>Proposed mechanisms of action for psychedelic treatments include: <ul style="list-style-type: none"> <li>Direct 5HT<sub>2A</sub> agonist/partial agonist effects</li> <li>bio-psychosocial-spiritual downstream effects of acute mind revealing experiences</li> </ul> </li> </ul>	High	No	5/9	2021	No	None identified

<ul style="list-style-type: none"> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> <li>▪ Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>○ increased brain-derived neurotrophic factor and neuroplasticity</li> <li>○ changes in the default mode network</li> <li>○ potential anti-inflammatory and anti-oxidant effects</li> <li>○ neurobiological effect of placebo</li> </ul>						
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ MDMA</li> <li>○ Psilocybin</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Depression</li> <li>○ Post-traumatic stress disorder</li> </ul> </li> </ul>	<p><a href="#">MDMA interactions with other drugs for depression may reduce the effectiveness of psychedelic-assisted therapy, but additional research is needed</a> (24)</p> <ul style="list-style-type: none"> <li>• MDMA interactions with monoamine reuptake inhibitors (including SSRIs) generally diminished effects, combining MDMA with serotonergic agents, particularly MAOIs, poses risks, and varied effects result from combining MDMA with stimulants, adrenergic agents, and dopamine blockade</li> <li>• Research on drug interactions with psilocybin is limited, but it is hypothesized that serotonin transporter (SERT) blockers are unlikely to affect its efficacy given that psilocybin's likely mechanism of action is reliant on direct serotonin receptor agonism rather than SERT activity</li> </ul>	High	No	3/9	2020	No	None identified
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ MDMA</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Post-traumatic stress disorder</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> <li>▪ Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<p><a href="#">MDMA-assisted psychotherapy was effective in reducing PTSD scores and reducing PTSD symptoms to below-diagnosis thresholds, and was found to be safe and well tolerated with some minor physical and psychological side effects</a> (13)</p> <ul style="list-style-type: none"> <li>• Experimental sessions included one to two six-to-eight-hour psychotherapy sessions, but the type of therapy was not reported</li> <li>• The evidence base has several limitations, including small sample sizes and lack of direct comparison to other drugs treating PTSD</li> </ul>	High	No	2/11	2021	No	None identified
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ MDMA</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Post-traumatic stress disorder</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Cognitive behavioural therapy</li> <li>○ Psychotherapy (general)</li> </ul> </li> </ul>	<p><a href="#">MDMA-assisted psychotherapy shows promise for PTSD treatment and has not shown any serious side effects or risk of addiction, but its availability might be limited due to factors like therapist qualifications and potential reimbursement challenges</a> (14)</p> <ul style="list-style-type: none"> <li>• MDMA is thought to work by enhancing serotonin, impacting receptors for self-confidence and anxiety reduction, increasing oxytocin for empathy, and elevating</li> </ul>	High	No	0/9	2020	No	None identified

<ul style="list-style-type: none"> <li>System features used to get treatment to those who need it <ul style="list-style-type: none"> <li>Delivery arrangements (how care is organized to get the treatment to people who need it) <ul style="list-style-type: none"> <li>Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>Who is providing/prescribing psychedelic-assisted psychotherapy</li> </ul> </li> </ul> </li> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> <li>Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<p>norepinephrine and dopamine to aid treatment, while also influencing fear extinction and altering brain activity</p> <ul style="list-style-type: none"> <li>Collectively, these mechanisms of action are thought to help psychotherapy by: <ul style="list-style-type: none"> <li>improving mood and reducing anxiety to facilitate therapy</li> <li>providing an opportunity for patients to see old problems from a new perspective</li> <li>stimulating patients to improve motivation to engage in therapy</li> <li>reducing hypervigilance associated with PTSD</li> <li>enabling patients to reflect on trauma without being overwhelmed</li> <li>improving patient-therapist relationship to help patients reflect on trauma and discuss patients' social and emotional relationships</li> <li>enhancing shared empathy and pro-social functioning</li> </ul> </li> <li>Therapeutic use of MDMA in controlled settings does not appear to present any large risks to patients, although risks of use in other contexts may include neurotoxicity, cognitive dysfunctions, potential polytoxicomania, moderate abuse risk and the danger of impure ecstasy, which may contain fatal additives</li> </ul>						
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>LSD</li> <li>MDMA</li> <li>Mescaline</li> <li>Psilocybin</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Post-traumatic stress disorder</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Cognitive behavioural therapy</li> <li>Psychotherapy (general)</li> </ul> </li> <li>System features used to get treatment to those who need it <ul style="list-style-type: none"> <li>Delivery arrangements (how care is organized to get the treatment to people who need it)</li> </ul> </li> </ul>	<p><a href="#">Effective preparation sessions in Substance-Assisted Psychotherapy (SAPT), involving therapeutic rapport, education on substance effects, and addressing logistics, interpersonal boundaries and intentions, may reduce resistance and enhance therapeutic effects</a> (1)</p> <ul style="list-style-type: none"> <li>Future research is needed to understand therapist factors and how they might influence treatment outcomes</li> </ul>	High	No	6/10	2021	No	None identified

<ul style="list-style-type: none"> <li>▪ Who is providing psychedelic-assisted psychotherapy</li> <li>▪ With what supports is psychedelic-assisted therapy provided</li> </ul> <ul style="list-style-type: none"> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> <li>▪ Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>							
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ LSD</li> <li>○ MDMA</li> <li>○ Mescaline</li> <li>○ Psilocybin</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Anxiety</li> <li>○ Depression</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Interpersonal therapy</li> </ul> </li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> <li>▪ Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<a href="#">Despite methodological limitations, early studies on psychedelic-assisted group therapy demonstrated safety and potential efficacy, with future research needed to refine protocols and assess outcomes with modern standards, emphasizing the importance of group settings in understanding responses to psychedelics (31)</a>	Medium	No	3/9	2018	No	None identified
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Ketamine</li> <li>○ LSD</li> <li>○ MDMA</li> <li>○ Psilocybin</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Post-traumatic stress disorder</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> </ul> </li> </ul> </li> </ul>	<a href="#">No included studies were identified for LSD or psilocybin, while limited evidence on ketamine or MDMA combined with psychotherapy suggested that future research is warranted (12)</a> <ul style="list-style-type: none"> <li>• Two small ketamine trials used mindfulness-based extinction and reconsolidation plus a single dose of ketamine, and it was found that those assigned to the ketamine groups had a longer duration of reduced PTSD symptoms by 24–30 days <ul style="list-style-type: none"> <li>○ No significant side effects were observed, but mild nausea was reported</li> </ul> </li> <li>• Four MDMA trials suggest that there is a positive effect from MDMA on PTSD compared to either active or inactive placebo controls in combination with psychotherapy <ul style="list-style-type: none"> <li>○ Each of the trials included preparatory sessions (ranging from two to 12), two to three experimental</li> </ul> </li> </ul>	High	No	7/10	2019	No	None identified

	<p>sessions lasting six to 10 hours, and integrative sessions following</p> <ul style="list-style-type: none"> <li>○ A reduction in PTSD symptoms was reported following the intervention</li> <li>○ Short-term side-effects of the drug included elevated blood pressure, pulse and body temperature, jaw tightness, nausea, feeling cold, dizziness, loss of appetite, impaired balance and irritability</li> <li>○ In one trial involving Veterans, four serious adverse events occurred, but only one was deemed as being possible related to the drug treatment: a premature ventricular contraction at baseline with an acute increase in ventricular contractions during experimental sessions</li> <li>○ In general, it is suggested that there is a positive effect from MDMA on PTSD compared to either active or inactive placebo controls in combination with psychotherapy</li> </ul>						
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ LSD</li> <li>○ Psilocybin</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Anxiety</li> <li>○ Depression</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Other (e.g., acceptance and commitment therapy, eye movement desensitization and reprocessing)</li> </ul> </li> </ul>	<p><a href="#">Third wave behavioural therapies such as dialectical behaviour therapy (DBT), acceptance and commitment therapy (ACT), and mindfulness based cognitive therapy (MBCT) demonstrated theoretical similarities with psychedelic therapy, suggesting their potential adjunctive use</a> (32)</p> <ul style="list-style-type: none"> <li>• More research is needed to understand dosage and effectiveness</li> </ul>	High	No	0/9	Published 2018	No	None identified
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ MDMA</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Post-traumatic stress disorder</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> <li>▪ Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<p><a href="#">MDMA-assisted psychotherapy was found to be a effective, durable and generally safe intervention for patients with chronic, treatment-refractory PTSD</a> (18)</p> <ul style="list-style-type: none"> <li>• Following the completion of MDMA assisted psychotherapy, participants were more likely to show a clinical response (RR = 3.47, 95% CI: 1.70, 7.06), remission (RR = 2.63, 95% CI: 1.37, 5.02), have a significant reduction in PTSD symptom scores (SMD= 1.30, 95% CI: 0.66, 1.94) and maintain this in extended follow-up ranging from two to 74 months (SMD = 1.10, 95% CI: 0.42, 1.78)</li> </ul>	High	No	9/11	Last searched December 2018	No	None identified

	<ul style="list-style-type: none"> <li>MDMA was well-tolerated, with few serious adverse events reported across studies</li> <li>MDMA dosage varied from 50 mg to 125 mg, and four studies allowed participants in the experimental groups to have a supplemental dose of MDMA (dosed at half the original dose strength) within two to three hours of the initial dose to boost the therapeutic effect</li> <li>There were no MDMA-related serious adverse events; however, one study reported four serious adverse events, including increased depressive symptoms and suicidal ideation, with three of the four deemed unrelated to the study drug</li> </ul>						
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>MDMA</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Post-traumatic stress disorder</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Psychotherapy (general)</li> </ul> </li> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> </ul> </li> </ul> </li> </ul>	<p><a href="#">MDMA-assisted psychotherapy had comparable treatment outcomes to prolonged exposure therapy, with a larger cumulative effect size on primary outcome measures with the MDMA-assisted psychotherapy, and similar effect sizes for secondary outcome measures</a> (33)</p> <ul style="list-style-type: none"> <li>MDMA-assisted psychotherapy had a considerably lower percentage of patients dropping out than prolonged exposure therapy did</li> <li>MDMA-assisted psychotherapy had larger effect sizes in both clinician-observed outcomes (not specified) than prolonged exposure therapy did (Hedges' <math>g=1.17</math> vs. <math>g=1.08</math>, respectively) and patient self-report outcomes (Hedges' <math>g=0.87</math> vs. <math>g=0.77</math>, respectively)</li> </ul>	High	No	4/11	Published July 2016	No	None identified
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Ketamine</li> <li>LSD</li> <li>MDMA</li> <li>Psilocybin</li> <li>Other: dipropyltryptamine (DPT)</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Depression</li> <li>Post-traumatic stress disorder</li> <li>Treatment-resistant depression</li> <li>Opioid addiction</li> <li>Tobacco addiction</li> <li>Alcohol use disorder</li> </ul> </li> </ul>	<p><a href="#">The efficacy of psychedelic-assisted psychotherapy over clinical outcomes in mostly chronic and refractory to treatments conditions reported response rates between 57 and 88%, remission rates between 18 and 85%, and those improvements were clinically relevant, sustained, observed in a short window of time and with fewer drug administrations and talk-therapy sessions compared to more established therapeutic options</a> (34)</p> <ul style="list-style-type: none"> <li>Across the literature, ketamine was delivered in different formats, normally including at least three preparation sessions, one drug session and at least one integration session</li> <li>When administered in residential settings, it may be complemented by other activities and may include an additional drug session</li> <li>Existential psychotherapy was the most cited model, using some principles of behavioural therapy</li> </ul>	High	No	4/9	Last searched September 2021	No	None identified

<ul style="list-style-type: none"> <li>○ Issues related to life-threatening conditions</li> <li>○ Social anxiety in autistic adults</li> <li>○ Demoralization in HIV-infected patients</li> <li>● Types of psychotherapy <ul style="list-style-type: none"> <li>○ Cognitive behavioural therapy (and cognitive behavioural conjoint therapy)</li> <li>○ Integrative therapy</li> <li>○ Interpersonal therapy</li> <li>○ Motivational enhancement therapy</li> <li>○ Psychotherapy (general)</li> <li>○ Other (e.g., acceptance and commitment therapy, eye movement desensitization and reprocessing)</li> <li>○ Assisted therapy plus mindfulness skills training</li> <li>○ Supportive-expressive group therapy</li> <li>○ Trauma interventions using mindfulness</li> <li>○ Extinction and reconsolidation</li> </ul> </li> <li>● System features used to get treatment to those who need it <ul style="list-style-type: none"> <li>○ Delivery arrangements (how care is organized to get the treatment to people who need it) <ul style="list-style-type: none"> <li>▪ Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>▪ Who is providing/prescribing psychedelic-assisted psychotherapy</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Medication-assisted psychotherapy included the use of LSD, dipropyltryptamine (DPT) and psilocybin</li> <li>● Medication-assisted psychotherapy proposes six to 12 hours of preparation, one drug session held by two trained facilitators and three integration sessions.</li> <li>● Therapists remain present during the whole duration of the session and will offer non-verbal psychological and medical support when needed</li> <li>● Bodywork techniques, mindfulness and sensorimotor psychotherapy were considered valuable tools for all phases of treatment</li> </ul>						
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<ul style="list-style-type: none"> <li>▪ Where psychedelic-assistance psychotherapy provided</li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes</li> <li>▪ Mental health outcomes</li> </ul> </li> </ul>							
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Ayahuasca brew</li> <li>○ Ibogaine</li> <li>○ Ketamine</li> <li>○ LSD</li> <li>○ MDMA</li> <li>○ Psilocybin</li> <li>○ Other: nitrous oxide</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Anxiety</li> <li>○ Depression</li> <li>○ Other: Substance use disorders, obsessive compulsive disorder</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Integrative therapy</li> <li>○ Motivational enhancement therapy</li> <li>○ Psychotherapy (general)</li> </ul> </li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> <li>▪ Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<p><a href="#">Psychedelic-assisted psychotherapy was associated with significant improvement in outcomes related to mental illnesses and no serious and long-term adverse events</a> (15)</p> <ul style="list-style-type: none"> <li>• Several combinations of psychedelic drugs, psychotherapy, and mental illnesses were identified, with psilocybin being the psychedelic substance most tested in the primary studies, manualized therapy (not defined) and non-directive support (not defined) being the psychotherapies most frequently evaluated, and anxiety and depression being the medical conditions that most primary studies evaluated</li> <li>• Overall, patients were followed up for one week to three years, when reported</li> <li>• Overall, MDMA-assisted psychotherapy for PTSD (eight primary studies) and psilocybin-assisted psychotherapy for treatment-resistant depression (seven primary studies) were the strategies most tested in the primary studies in the systematic reviews</li> <li>• In general, the therapeutic effects seemed to last for week or months after one to three treatment sessions and no severe adverse events were reported in the primary studies</li> <li>• Systematic reviews concluded that, in general, psychedelic drugs were associated with significant improvement in outcomes related to mental illnesses and no serious and long-term adverse events were reported in the primary studies</li> </ul>	High	No	5/9	Last searched 4 May 2021	No	None identified
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Psilocybin</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Depression</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> <li>• Outcomes</li> </ul>	<p><a href="#">Psychotherapy with psilocybin showed a significant reduction in depressive symptoms after treatment with one or two doses</a> (26)</p> <ul style="list-style-type: none"> <li>• Symptomatic improvement was immediate in some cases, showing significant results one day and one week after the second dose</li> <li>• Health improvement was long-lasting, maintaining significant reduction up to six, eight and 12 months</li> <li>• The consumption of psilocybin or any psychoactive substance can produce psychotic symptoms such as</li> </ul>	High	No	4/9	Last searched April 2022	No	None identified



<ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> <li>Safety (adverse events)</li> </ul> </li> </ul>	<p>delusions, panic attacks and depersonalization; however, when carried out in a controlled context, adverse effects were mild or moderate, transient and limited (headaches, dizziness, nausea and tachycardia)</p> <ul style="list-style-type: none"> <li>Psilocybin had a low addictive risk and no evidence that it caused any withdrawal symptoms</li> <li>The range of psilocybin doses went from a moderate dose of 10 mg in the first sessions to high doses of 30 mg/70 kg in the second sessions</li> </ul>						
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Ketamine</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Anxiety</li> <li>Depression</li> <li>Post-traumatic stress disorder</li> <li>Other: obsessive compulsive disorder, bipolar disorder, attention-deficit hyperactivity disorder, eating disorder substance use disorder</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Motivational enhancement therapy</li> <li>Cognitive behavioural therapy</li> <li>Other: functional analytic psychotherapy, mindfulness-based intervention</li> </ul> </li> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> </ul> </li> </ul> </li> </ul>	<p><a href="#">Ketamine-assisted psychotherapy may be effective in initiating rapid, significant benefits for major depression disorder, PTSD, attention-deficit hyperactivity disorder, generalized anxiety disorder, obsessive-compulsive disorder and substance use disorder</a> (8)</p> <ul style="list-style-type: none"> <li>Overall, it appears that higher doses of ketamine, more frequent ketamine-assisted psychotherapy sessions and longer durations of psychotherapy increase the efficacy and durability of improvements within patients with a range of disorders</li> <li>However, considering the heterogeneity of populations studied, it is not possible to recommend one psychotherapeutic modality over another or an ideal number of sessions</li> </ul>	High	No	4/10	Last searched November 2021	No	None identified
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Ketamine</li> <li>LSD</li> <li>MDMA</li> <li>Psilocybin</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Depression</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Psychotherapy (general)</li> </ul> </li> </ul>	<p><a href="#">Conventional antidepressants and especially psychedelics may significantly improve the treatment of different mental disorders and enhance the efficacy of psychotherapy</a> (35)</p> <ul style="list-style-type: none"> <li>Combinations of psychotherapy with antidepressants, psychedelics, MDMA and ketamine are complex, involving bidirectional and potentially synergistic interactions</li> <li>Overall, LSD and psilocybin appear to be among the least dangerous drugs for recreational users, even in comparison to those with well-established medical uses</li> </ul>	High	No	1/9	Last searched 1 January 2020	No	None identified

<ul style="list-style-type: none"> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> <li>Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>like benzodiazepines, in terms of both harm to users and harm to others</li> <li>The potential for addiction was considered to be especially low</li> </ul>						
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Psilocybin</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Depression</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Psychotherapy (general)</li> </ul> </li> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> <li>Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<p><a href="#">Psilocybin-assisted therapy compared to control resulted in a significantly greater antidepressant effect at the primary endpoint from baseline, independent of diagnosis or type of control</a> (27)</p> <ul style="list-style-type: none"> <li>The standard mean difference (SMD) between experimental and control arms in depression outcomes across all included studies was <math>-0.78</math> (95% CI: <math>[-1.06, -0.51]</math>, <math>P &lt; 0.00001</math>), indicating a large and significant effect</li> <li>Response rates RRs favoured the psilocybin group over the control (RR: 2.63, 95% CI: <math>[1.84, 3.77]</math>, <math>P &lt; 0.00001</math>), with a pooled response rate of 136/238 (57%) in the treatment group versus 52/236 (22%) in the control group</li> </ul>	High	No	6/11	Last searched 11 January 2023	No	None identified
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Ibogaine</li> <li>LSD</li> <li>Psilocybin</li> </ul> </li> <li>Type of psychotherapy <ul style="list-style-type: none"> <li>Psychotherapy (general)</li> </ul> </li> <li>Priority populations <ul style="list-style-type: none"> <li>People with mental-health issues</li> </ul> </li> <li>Outcomes</li> <li>Mental health outcomes</li> </ul>	<p><a href="#">Very few small-scale studies provide preliminary support for the use of psilocybin to support those with PTSD and treatment-resistant depression</a> (28)</p> <ul style="list-style-type: none"> <li>Only one study examined psilocybin's effects on PTSD among a small group of older, long-term AIDS survivors and found the severity of PTSD reduced from baseline, which was maintained at three-month follow-up</li> <li>Four studies reported that psilocybin assisted therapy reduced depressive symptoms in patients with treatment-resistant depression and in cancer patients</li> <li>No studies have investigated the potential of LSD or ibogaine as monotherapies for PTSD</li> </ul>	High	No	0/9	Published 2022	No	Race/ethnicity/culture/language  Personal characteristic associated with discrimination
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Ibogaine</li> <li>MDMA</li> <li>Psilocybin</li> </ul> </li> <li>Outcomes</li> <li>Health outcomes</li> </ul>	<p><a href="#">There is a lower rate of representation of people of colour in studies related to the effectiveness of psychedelic-assisted therapy, leading to a lack of generalizability of findings from studies to other populations</a> (36)</p> <ul style="list-style-type: none"> <li>People of colour experience psychological distress at a rate equal to and sometimes higher than non-Hispanic Whites, in particular reporting higher levels of PTSD</li> <li>Of studies of psychedelic-assisted psychotherapy approximately 82.3% of all participants are non-Hispanic White, which skewed compared to the relative demographics of the countries in which studies are undertaken</li> </ul>	High	No	2/9	Published 2018	No	Race/ethnicity/culture/language

<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ MDMA</li> </ul> </li> <li>• Type of psychotherapy <ul style="list-style-type: none"> <li>○ Other: non-directive therapy</li> </ul> </li> <li>• System features used to get treatment to those who need it <ul style="list-style-type: none"> <li>○ Delivery arrangements <ul style="list-style-type: none"> <li>▪ Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>▪ With what supports is psychedelic-assisted therapy provided</li> </ul> </li> </ul> </li> <li>• Priority populations <ul style="list-style-type: none"> <li>○ People with mental-health issues</li> </ul> </li> <li>• Health outcomes <ul style="list-style-type: none"> <li>○ Mental health outcomes</li> </ul> </li> <li>• Safety (adverse events)</li> </ul>	<p><a href="#">Phase 2 clinical trials offer some support for the use of MDMA-assisted psychotherapy for treatment-resistant PTSD, but additional clinical trials are needed</a> (19)</p> <ul style="list-style-type: none"> <li>• The review included six Phase 2 clinical trials for MDMA-assisted psychotherapy for PTSD</li> <li>• Participants had to have a diagnosis of PTSD and had treatment-resistant symptoms following three months of antidepressant treatment and at least six months of psychotherapy</li> <li>• Participants were provided with preparatory non-drug psychotherapy followed by three eight-hour MDMA-assisted psychotherapy sessions using a nondirective approach</li> <li>• The study found reduced psychological trauma and long-term remission with no serious drug-related adverse events and no adverse neurocognitive effects</li> </ul>	High	No	3/9	Literature last reviews 2019	No	None identified
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Ketamine</li> <li>○ LSD</li> <li>○ MDMA</li> <li>○ Psilocybin</li> </ul> </li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes</li> <li>○ Care experiences</li> </ul> </li> </ul>	<p><a href="#">Insufficient evidence was identified to determine the effects of psychedelic-assisted psychotherapy on a range of mental health conditions</a> (9)</p> <ul style="list-style-type: none"> <li>• The review found 25 studies, about half of which investigated stand-alone treatments (cannabis and ketamine), while the other half investigated adjunct treatment (MDMA, LSD and psilocybin)</li> <li>• The quality of the studies was reportedly mixed, and all but one category of evidence – ketamine for depression – was allocated an unknown ranking including MDMA for treating PTSD, LSD for treating anxiety, LSD for treating depression, psilocybin for treating anxiety and psilocybin for treating depression</li> </ul>	Medium	No	9/11	Literature last reviewed 2017	No	None identified
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Psilocybin</li> </ul> </li> <li>• Types of mental health conditions <ul style="list-style-type: none"> <li>○ Depression</li> </ul> </li> </ul>	<p><a href="#">Treatment-resistant depression responds best to higher doses of psilocybin (around 40 mg/70 kg), but patients with comorbid anxiety and depression may respond best to lower doses</a> (29)</p> <ul style="list-style-type: none"> <li>• The review examined the dose-response relationship of psilocybin on anxiety and depression and examined the possible side effects of its use</li> </ul>	High	No	7/11	Literature last reviewed 2023	No	None identified

<ul style="list-style-type: none"> <li>○ Anxiety</li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Other (non-directive psychotherapy)</li> </ul> </li> <li>• System features used to get treatment to those who need it <ul style="list-style-type: none"> <li>○ Delivery arrangements <ul style="list-style-type: none"> <li>▪ Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>▪ Where psychedelic-assisted psychotherapy is provided</li> </ul> </li> </ul> </li> <li>• Priority populations <ul style="list-style-type: none"> <li>○ People with mental-health issues</li> </ul> </li> <li>• Outcomes <ul style="list-style-type: none"> <li>○ Mental health outcomes</li> </ul> </li> <li>• Safety (adverse events)</li> </ul>	<ul style="list-style-type: none"> <li>• Treatment-resistant depression was defined by a lack of response to two to four antidepressant trials at sufficient dose of more than eight-week duration</li> <li>• Psilocybin was administered orally in capsules (with the mean dose when delivered as a single dose 16.5 mg/70 kg and for studies with two doses 31.5 mg/70 kg) during an individual psychedelic-assisted psychotherapy setting where non-directive supportive psychotherapy was provided</li> <li>• Participants reported not having taken antidepressant for at least two weeks prior to psilocybin use</li> <li>• The mean length of time between a first and second session of psilocybin was 3.54 weeks (with a range of two to eight weeks)</li> <li>• Half of psilocybin antidepressant effect was found to occur at doses of 10.13 mg/70 kg and 95% of the antidepressant effect occurs at doses of 41.14 mg/70 kg, but when excluding one study focused on treatment-resistant depression the 95% of the antidepressant effect dropped to 25.05 mg/70 kg</li> <li>• For adverse events, physical discomfort and elevation of blood pressure was encountered with an increasing dose as well as transient, mild to moderate headache and nausea</li> <li>• For psychological discomfort, all panic reactions occurred while on psychedelics and were handled with immediate psychological support; these most frequently took place when ingesting the highest dosage</li> </ul>						
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Ketamine</li> </ul> </li> <li>• Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Post-traumatic stress disorder</li> </ul> </li> <li>• Types of psychotherapy <ul style="list-style-type: none"> <li>○ Other: mindfulness based extinction and reconsolidation therapy</li> </ul> </li> <li>• System features used to get treatment to those who need it <ul style="list-style-type: none"> <li>○ Design of psychedelic-assisted psychotherapy (e.g.,</li> </ul> </li> </ul>	<p><a href="#">Few studies with small included population demonstrate that Ketamine when combined with psychotherapy may reduce symptoms of PTSD</a> (10)</p> <ul style="list-style-type: none"> <li>• Systematic review and meta-analysis included four studies with 38 participants in total and used several ketamine administration protocols</li> <li>• In two of the included studies, patients received 12 sessions over ten weeks using mindfulness based extinction and reconsolidation therapy alongside a single dose of ketamine administered at the time of psychotherapy</li> <li>• A third study provided 10 weeks of prolonged exposure therapy alongside three weekly doses of ketamine administered 24 hours prior to the first three session</li> </ul>	High	No	5/11	Literature last reviewed 2021	Yes	None identified

<ul style="list-style-type: none"> <li>access and eligibility, package of care or care pathways for those that are eligible) <ul style="list-style-type: none"> <li>Where psychedelic-assisted psychotherapy is provided</li> </ul> </li> <li>Outcomes <ul style="list-style-type: none"> <li>Health outcomes <ul style="list-style-type: none"> <li>Mental health outcomes</li> <li>Safety</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>The fourth study, patients received five daily sessions of exposure therapy over the course of a single ketamine infusion</li> <li>All studies demonstrated significant reduction in symptoms</li> </ul>						
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>MDMA</li> <li>Psilocybin</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Anxiety</li> <li>Depression</li> <li>Post-traumatic stress disorder</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Acceptance and commitment therapy</li> <li>Other (prolonged exposure therapy)</li> </ul> </li> <li>System features used to get treatment to those who need it <ul style="list-style-type: none"> <li>Delivery arrangements <ul style="list-style-type: none"> <li>Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>Where psychedelic-assisted psychotherapy is provided</li> <li>With what supports is psychedelic-assisted therapy provided</li> </ul> </li> </ul> </li> <li>Priority populations</li> </ul>	<p><a href="#">RCTs demonstrate some potential for the use of MDMA to reduce PTSD symptoms and psilocybin for treatment-resistant depression</a> (20)</p> <ul style="list-style-type: none"> <li>Psychedelic assisted psychotherapy typically includes three types of sessions, preparatory sessions, medication (one to three sessions with moderate to high doses of a psychedelic), and integration sessions</li> <li>Drugs are typically administered in a comfortable room with a reclining chair or bed and the therapist listens empathetically for the next six to eight hours</li> <li>Types of psychotherapy have not been assessed against one another but widely accepted therapies include prolonged exposure therapy, cognitive processing therapy and acceptance and commitment therapy, while less structured treatments include dynamic therapy and psychoanalysis</li> <li>Controlled trials suggested a significant and sustained reduction in PTSD symptoms severity at three years following two psychedelic sessions using MDMA</li> <li>Controlled trials of psilocybin for treatment-resistant depression (using 10 mg and 25 mg two weeks later) resulted in a reduction in depressive symptoms</li> <li>Two very small trials showed reductions in major depression (that had failed at least one previous antidepressant) up to three weeks after drug administration</li> </ul>	No	High	3/9	Literature last searched 2019	No	None identified

<ul style="list-style-type: none"> <li>○ People with mental-health issues</li> <li>○ People with substance-use issues</li> <li>● Outcomes <ul style="list-style-type: none"> <li>○ Mental health outcomes</li> </ul> </li> </ul>							
<ul style="list-style-type: none"> <li>● Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ Ayahuasca</li> <li>○ Ibogaine</li> <li>○ MDMA</li> <li>○ Psilocybin</li> <li>○ Other (5-MeO-DMT)</li> </ul> </li> <li>● Types of mental-health conditions <ul style="list-style-type: none"> <li>○ Depression</li> <li>○ Post-traumatic stress disorder</li> <li>○ Other: obsessive compulsive disorder, social anxiety, opioid use disorder, alcohol use disorder, tobacco use, mixed substance use disorders and mood symptoms</li> </ul> </li> <li>● Types of psychotherapy</li> <li>● Psychotherapy (general)</li> </ul>	<a href="#">MDMA coupled with psychotherapy co-led by two mental-health professionals may reduce PTSD symptom severity and lead to clinically meaningful improvements in the short term</a> (2) <ul style="list-style-type: none"> <li>● Psilocybin-assisted psychotherapy may reduce severity of depression and result in sustained remission for some participants, but these benefits were not observed when psilocybin-assisted therapy was compared to intensive psychotherapy and daily escitalopram</li> <li>● Ayahuasca use may be associated with a short-term reduction in depression symptoms and suicidality (low strength of evidence)</li> <li>● Studies conducted in the US have mostly included non-Veteran, young, non-Hispanic white populations with access to a clinical research center or treatment program</li> <li>● Applicability of benefits in more diverse populations and treatment settings is unclear</li> </ul>	High	Not Living	9/9	2022	No	Race/ethnicity/culture/language
<ul style="list-style-type: none"> <li>● Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>○ MDMA</li> </ul> </li> <li>● Types of mental-health conditions <ul style="list-style-type: none"> <li>○ PTSD</li> </ul> </li> <li>● Types of psychotherapy <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> <li>● Outcomes <ul style="list-style-type: none"> <li>○ Health outcomes <ul style="list-style-type: none"> <li>▪ Mental health outcomes</li> <li>▪ Safety (adverse events)</li> </ul> </li> </ul> </li> </ul>	<a href="#">Protocol for a systematic review examining the use of MDMA as an adjunct to psychotherapy for the treatment of PTSD</a> (37) <ul style="list-style-type: none"> <li>● Protocol for a Cochrane review examining the use of MDMA as an adjunct to psychotherapy delivered by a licenced psychotherapist with previous experience treating PTSD</li> <li>● Review will include RCTs of adult participants who have a diagnosis of PTSD (defined as a duration of symptoms for more than six months and a score of 40 or more on a CAPS-4), however it will exclude studies with co-morbid conditions</li> <li>● All included studies must have experience groups receiving a minimum of one MDMA dosing session along with individual psychotherapy</li> </ul>	High	No	No rating available for this type of document	Protocol	No	None identified

## Appendix 4: Key findings from single studies related to the use of psychedelic-assisted psychotherapy for Veterans

Dimension of the organizing framework	Study characteristics	Sample and intervention description	Declarative title and key findings
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>Ketamine</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Post-traumatic stress disorder</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Other (e.g., acceptance and commitment therapy, eye movement desensitization and reprocessing)</li> </ul> </li> </ul>	<p><i>Focus of study:</i> To assess the feasibility of combining prolonged exposure therapy with repeated ketamine administration in PTSD</p> <p><i>Publication date:</i> 2020</p> <p><i>Jurisdiction studied:</i> United States</p> <p><i>Methods used:</i> 10-week pilot study</p>	<p>Veterans aged 18–75 years with chronic and moderate to severe PTSD.</p> <p>Intravenous ketamine (0.5 mg/kg) administered 24 hours prior to weekly prolonged exposure therapy.</p>	<p><a href="#">Repeated IV ketamine administration was able to be used concurrently with prolonged exposure therapy to treat PTSD</a> (38)</p>
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy <ul style="list-style-type: none"> <li>MDMA</li> </ul> </li> <li>Types of mental-health conditions <ul style="list-style-type: none"> <li>Post-traumatic stress disorder</li> </ul> </li> <li>Types of psychotherapy <ul style="list-style-type: none"> <li>Other (non-directive therapy)</li> </ul> </li> <li>System features used to get treatment to those who need it <ul style="list-style-type: none"> <li>Delivery arrangements <ul style="list-style-type: none"> <li>Design of psychedelic-assisted psychotherapy</li> </ul> </li> </ul> </li> </ul>	<p><i>Focus of study:</i> MDMA-assisted psychotherapy for PTSD</p> <p><i>Publication date:</i> 2018</p> <p><i>Jurisdiction studied:</i> United States</p> <p><i>Methods used:</i> RCT</p>	<p>Twenty-six service personnel (Veterans and first responders) with chronic PTSD duration of six-months or more and had a clinician-administered PTSD scale total score of 50 or greater.</p> <p>Participants were randomly assigned to one of three different doses of MDMA and psychotherapy: 30mg, 75mg or 125 mg. MDMA was administered orally in two-eight-hour sessions with non-directive psychotherapy and were assessed 12 months later. The first MDMA session was preceded by three 90-minute psychotherapy sessions with a co-therapy team. In total the</p>	<p><a href="#">Active doses (75 mg and 125 mg) of MDMA with adjunctive psychotherapy in a controlled setting were effective and well tolerated in reducing PTSD symptoms in Veterans and first responders</a> (23)</p> <ul style="list-style-type: none"> <li>MDMA-assisted psychotherapy with 75 mg or 125 mg resulted in significant improvements of PTSD symptoms in Veterans and first responders with chronic PTSD that had failed previous treatment</li> <li>Participants in the comparator group of 30 mg receiving the same psychotherapy had significantly less symptoms remission than the active dose groups of 75 mg and 125 mg</li> <li>The 75 mg dose led to larger decreases in symptoms than the 125 mg dose, however authors note that this might have to do with the small sample size</li> <li>Severity of depression symptoms was significant reduced for the 125 mg group but not for the 70 mg group when compared with the 30 mg group</li> <li>Sleep quality and dissociative symptoms also significant improved for both active dose groups</li> </ul>



Dimension of the organizing framework	Study characteristics	Sample and intervention description	Declarative title and key findings
<ul style="list-style-type: none"> <li>▪ Who is providing/prescribing psychedelic-assisted psychotherapy</li> <li>▪ Where psychedelic-assisted psychotherapy is provided</li> <li>• Priority conditions that may face safety concerns               <ul style="list-style-type: none"> <li>○ Suicide risk</li> </ul> </li> <li>• Priority populations               <ul style="list-style-type: none"> <li>○ Veterans</li> </ul> </li> <li>• Outcomes               <ul style="list-style-type: none"> <li>○ Mental health outcomes</li> <li>○ Safety (adverse events)</li> </ul> </li> </ul>		<p>treatment included 18 hours of non-drug psychotherapy and 16–24 hours (two to three sessions) of MDMA-assisted psychotherapy.</p>	<ul style="list-style-type: none"> <li>• Few adverse events took place and were limited to mild to moderate jaw clenching and perspiration, while suicidal ideation remained the same among all groups</li> </ul>
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy               <ul style="list-style-type: none"> <li>○ Ibogaine</li> <li>○ Other: 5-MeO-DMT</li> </ul> </li> <li>• Types of mental-health conditions               <ul style="list-style-type: none"> <li>○ Anxiety</li> <li>○ Depression</li> <li>○ Post-traumatic stress disorder</li> </ul> </li> <li>• Types of psychotherapy               <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> </ul>	<p><i>Focus of study:</i> To examine the effectiveness of psychedelic-assisted therapy in trauma-exposed U.S. Special Operations Forces Veterans (SOFV) seeking treatment for cognitive and mental health problems at a therapeutic program in Mexico.</p> <p><i>Publication date:</i> 2023</p> <p><i>Jurisdiction studied:</i> Mexico</p> <p><i>Methods used:</i> Open-label study, self-reported clinical assessment</p>	<p>Eighty-six trauma-exposed U.S. SOFVs at a treatment centre in Mexico.</p> <p>Clinical program collected prospective clinical program evaluation data through online surveys at four timepoints (baseline/pre-treatment and one-, three- and six-months after treatment) from September 2019 to March 2021.</p>	<p><a href="#">Data suggests that combined ibogaine and 5-MeO-DMT assisted therapy has the potential to provide rapid improvements in mental health functioning</a> (5)</p> <p>The study found significant and large improvements in self-reported PTSD symptoms (<math>p &lt; .001</math>, <math>d = .414</math>), depression (<math>p &lt; .001</math>, <math>d = .275</math>), anxiety (<math>p &lt; .001</math>, <math>d = .276</math>), insomnia severity (<math>p &lt; .001</math>, <math>d = .351</math>), post-concussive symptoms (<math>p &lt; .001</math>, <math>d = .389</math>) and satisfaction with life (<math>p &lt; .001</math>, <math>d = .371</math>) from baseline to one-month follow-up with sustained clinical benefit at three-month and six-month follow-ups</p>



Dimension of the organizing framework	Study characteristics	Sample and intervention description	Declarative title and key findings
<ul style="list-style-type: none"> <li>System features used to get treatment to those who need it               <ul style="list-style-type: none"> <li>Delivery arrangements (how care is organized to get the treatment to people who need it)                   <ul style="list-style-type: none"> <li>Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>Where psychedelic-assistance psychotherapy is provided</li> <li>With what supports is psychedelic-assisted therapy provided</li> </ul> </li> </ul> </li> </ul>			
<ul style="list-style-type: none"> <li>Type of psychedelic drugs used as part of psychotherapy               <ul style="list-style-type: none"> <li>Ibogaine</li> <li>Other: 5-MeO-DMT</li> </ul> </li> <li>Types of mental-health conditions               <ul style="list-style-type: none"> <li>Anxiety</li> <li>Depression</li> </ul> </li> </ul>	<p><i>Focus of study:</i> Secondary data analysis to understand the impacts of baseline predictors on treatment outcomes among U.S. SOFVs who completed a combined ibogaine- and 5-MeO-DMT-assisted treatment program in Mexico and assess psychedelic influence on enduring positive mental health changes up to 6 months after treatment.</p> <p><i>Publication date:</i> 2023</p>	<p>Eighty-six trauma-exposed U.S. SOFVs at a treatment centre in Mexico. Patients were asked to complete surveys at four time points: pre-treatment (before arriving at the clinic) and one-, three- and six-month(s) post-treatment.</p>	<p><a href="#">Combined ibogaine and 5-MeO-DMT therapy has significant potential to address stress- and trauma-related issues in the SOFV population</a> (4)</p> <ul style="list-style-type: none"> <li>Younger age and higher baseline depression and anxiety severity were correlated with larger improvements in satisfaction with life, cognitive functioning, psychological flexibility and trauma symptoms from pre-treatment to one-month follow-up</li> <li>The changes in consciousness and psychological flexibility caused by psychedelics appear to be critical factors associated</li> </ul>

Dimension of the organizing framework	Study characteristics	Sample and intervention description	Declarative title and key findings
<ul style="list-style-type: none"> <li>○ Post-traumatic stress disorder</li> <li>• Types of psychotherapy               <ul style="list-style-type: none"> <li>○ Psychotherapy (general)</li> </ul> </li> <li>• System features used to get treatment to those who need it               <ul style="list-style-type: none"> <li>○ Delivery arrangements (how care is organized to get the treatment to people who need it)                   <ul style="list-style-type: none"> <li>▪ Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>▪ Where psychedelic-assistance psychotherapy is provided</li> <li>▪ With what supports is psychedelic-assisted therapy provided</li> </ul> </li> </ul> </li> </ul>	<p><i>Jurisdiction studied:</i> Mexico</p> <p><i>Methods used:</i> Open-label study, self-reported clinical assessment</p>		<p>with positive outcomes, along with younger age and greater anxiety/depression symptom severity before treatment</p>
<ul style="list-style-type: none"> <li>• Type of psychedelic drugs used as part of psychotherapy               <ul style="list-style-type: none"> <li>○ Psilocybin</li> </ul> </li> <li>• Types of mental-health conditions</li> </ul>	<p><i>Focus of study:</i> To understand veterans' experiences when accessing treatment for trauma symptoms and potential motivators to use psilocybin. The study also aimed to explore veterans' perceived effect of psilocybin on their trauma symptoms.</p>	<p>Veterans, over the age of 18, with self-reported current or previous PTSD symptoms, who reported either having used or considered using psilocybin.</p>	<p><a href="#">Three themes were identified that answered the research question: dislike for prescribed medication, desperation facilitating use of psychedelics, and both immediate and long-term benefits of psychedelics</a> (30)</p>

Dimension of the organizing framework	Study characteristics	Sample and intervention description	Declarative title and key findings
<ul style="list-style-type: none"> <li>○ Post-traumatic stress disorder</li> <li>● System features used to get treatment to those who need it               <ul style="list-style-type: none"> <li>○ Delivery arrangements (how care is organized to get the treatment to people who need it)                   <ul style="list-style-type: none"> <li>▪ Design of psychedelic-assisted psychotherapy (e.g., access and eligibility, package of care or care pathways for those that are eligible)</li> <li>▪ Who is providing/prescribing psychedelic-assisted psychotherapy</li> <li>▪ Where psychedelic-assistance psychotherapy is provided</li> <li>▪ With what supports is psychedelic-assisted therapy provided</li> </ul> </li> </ul> </li> </ul>	<p><i>Publication date:</i> 2022</p> <p><i>Jurisdiction studied:</i> United States, United Kingdom</p> <p><i>Methods used:</i> Interpretative phenomenological analysis</p>		<ul style="list-style-type: none"> <li>● All participants reported barriers in accessing PTSD treatment; these included experiencing shame or guilt and long wait lists for therapies</li> <li>● All participants reported a dislike for prescribed medication</li> <li>● Desperation was evident some participants decision to try psychedelics, with one participant reporting: “I had become very frustrated with the lack of options available to me, and I had nowhere else to go”</li> <li>● All participants who had used psilocybin reported beneficial immediate and long-lasting effects; this seemed to be strongly associated with changes of perception, learning and symptom reduction</li> </ul>

## Appendix 5: Detailed jurisdictional scan about health-system arrangements for psychedelic-assisted psychotherapy for Veterans in each of the ‘Five Eyes’ countries

Jurisdiction	Description of program
Australia	<ul style="list-style-type: none"> <li>As of 1 July 2023, <a href="#">psychiatrists in Australia are able to prescribe MDMA and psilocybin</a> for controlled clinical use, including for the treatment of PTSD and treatment-resistant depression</li> <li>Access to the drugs requires <a href="#">pre-approval via the Therapeutic Goods Administration</a> and must be taken in a controlled medical setting in combination with psychotherapy (not specific) <ul style="list-style-type: none"> <li>There is currently no coverage under the <a href="#">Medicare benefits schedule</a></li> </ul> </li> <li>Psychiatrists administering the drugs must be <a href="#">approved under the authorized prescriber scheme</a> with approval by a human research ethics committee</li> <li>In addition to this pathway, there are also ongoing clinical trials for both psilocybin and MDMA in which individuals can register, and this includes an ongoing trial by Phoenix Australia for ex-serving Australian Defence Force personnel and first responders</li> </ul>
Canada	<ul style="list-style-type: none"> <li>As of May 2023, according to Medavie Blue Cross Canada – the insurer of health services for Veterans in Canada – psychedelic-assisted psychotherapy is an emerging/experimental therapy and is not recognized as a Veterans Affairs Canada approved treatment</li> <li>A Senate report released in November 2023, is asking Veterans Affairs Canada and the Department of National Defence, in collaboration with Health Canada and the Canadian Institutes of Health Research to launch 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</li> <li>In June 2023, the <a href="#">federal government invested \$3 million in three clinical trials</a> (through the Canadian Institutes of Health Research) on the use of psilocybin-assisted psychotherapy <ul style="list-style-type: none"> <li>The three trials will <a href="#">examine psilocybin-assisted psychotherapy to treat</a> 1) alcohol-use disorders, 2) treatment-resistant depression and 3) end-of-life psychological distress in advanced-stage cancer patients</li> </ul> </li> <li>Though not specific to Veterans as of December 2021, an amendment was made to the <a href="#">special access program</a> permitting requests for restricted drugs, which would include some psychedelics like psilocybin and MDMA <ul style="list-style-type: none"> <li><a href="#">Requests must be made by an individual’s physician</a> (or in some provinces or territories other providers with prescribing privileges) and can only be used to treat an individual with <a href="#">“a serious or life-threatening condition where conventional treatments have failed, are unsuitable or are not available in Canada”</a></li> <li>To provide the treatment providers must maintain credible records including quantities of the drug received and any adverse reactions</li> <li>There are currently two suppliers of psychedelics that may be accessed in Canada</li> </ul> </li> </ul>
New Zealand	<ul style="list-style-type: none"> <li>Unable to identify any use of psychedelic-assisted therapies</li> </ul>
United Kingdom	<ul style="list-style-type: none"> <li>Psilocybin other psychedelics remain illegal in the U.K. and there is currently no single-access program for U.K. Veterans <ul style="list-style-type: none"> <li>Ketamine is legal but remains a controlled substance for which a prescription is required</li> </ul> </li> <li>These drugs may be used as part of research studies, which with a successful application are exempt from many of the rules around schedule 1 and 2 drugs</li> <li>Relatively <a href="#">small randomized controlled trials have been undertaken in the U.K.</a>, where psilocybin has been provided alongside non-directive psychotherapy and followed by participation in cognitive processing therapy (a type of cognitive behavioural therapy) provided between doses</li> <li>In addition, select U.K.-based charity <a href="#">Heroic Hearts Project</a> runs retreats in Jamaica, Mexico and Peru where participants are able to use ayahuasca or psilocybin while participating in group therapy <ul style="list-style-type: none"> <li>This work is done in partnership with researchers at Imperial College London</li> </ul> </li> <li>Though not Veteran-specific, the Medicine and Healthcare products Regulatory Agency fast-tracked the designation of ketamine-assisted therapy for the treatment of severe alcohol use disorder under the Innovative Licensing and Access Pathway, which is used to accelerate time to market</li> </ul>

	<ul style="list-style-type: none"> <li>○ However, its use in the form of a nasal spray (as esketamine) has not been recommended by the <a href="#">National Institute for Health and Care Excellence</a> for treatment-resistant depression and is therefore not publicly covered</li> </ul>
United States	<ul style="list-style-type: none"> <li>● In 2017 and 2019, the U.S. Food and Drug Administration granted breakthrough therapy designation to MDMA and psilocybin, which is designed to expedite the development and review of drugs intended to treat a serious condition and where preliminary evidence indicates that the drug may demonstrate substantial improvement over available therapy on clinically significant endpoints</li> <li>● Though Veterans Affairs in the U.S. does not currently provide psychedelic-assisted therapy, there are two ways that Veterans may be able to access these services</li> <li>● The first is through charitable organizations such as <a href="#">VETS</a>, which offer resources and grants for U.S. Special Operations Forces Veterans with combat deployments after 11 September 2001 to receive psychedelic-assisted therapy treatment outside the U.S. as well as preparation and integration coaching and ongoing community support <ul style="list-style-type: none"> <li>○ Psychedelics include <a href="#">ibogaine, ketamine, psilocybin, MDMA, 5-MeO-DMT and ayahuasca</a></li> <li>○ <a href="#">Healing grant recipients</a> receive weekly meditation classes, access to a community platform, workshops in advance of the psychedelic assisted therapy, grant funding to pay for the psychedelic assisted therapy, international travel support, preparation and coaching classes and group integration coaching</li> <li>○ <a href="#">Heroic Hearts Project</a> similarly hosts monthly retreats to help Veterans with PTSD</li> </ul> </li> <li>● The second way is through clinical trials currently being run through the U.S. Department of Veterans Affairs which are examining the effectiveness of psychedelic drugs including MDMA and psilocybin as treatments for PTSD, action and other serious mental health issues</li> <li>● In 2022, two congressmen announced the launch of the Congressional Psychedelics Advancing Clinical Treatments (PACT) caucus, which aims to alleviate the national mental health crisis through psychedelic science and research</li> </ul>

## Appendix 6: Documents excluded at the final stages of reviewing

Document type	Hyperlinked title
Reviews that do not meet minimum standard for an evidence synthesis	<a href="#">A review of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy</a>
	<a href="#">Assessment and management of patients at risk for suicide: Synopsis of the 2019 U.S. Department of Veterans Affairs and U.S. Department of Defense clinical practice guidelines</a>
	<a href="#">breakthrough for trauma treatment: Safety and efficacy of MDMA-assisted psychotherapy compared to paroxetine and sertraline</a>
	<a href="#">Ethical and practical considerations for the use of psychedelics in psychiatry</a>
	<a href="#">Exploring psilocybin-assisted psychotherapy in the treatment of methamphetamine use disorder</a>
	<a href="#">MDMA and PTSD treatment: “PTSD: From novel pathophysiology to innovative therapeutics”</a>
	<a href="#">MDMA-assisted psychotherapy for post-traumatic stress disorder: The devil is in the detail</a>
	<a href="#">MDMA-assisted psychotherapy for PTSD: Are memory reconsolidation and fear extinction underlying mechanisms?</a>
	<a href="#">MDMA-assisted psychotherapy for PTSD: Growing evidence for memory effects mediating treatment efficacy</a>
	<a href="#">MDMA-assisted psychotherapy with adolescents suffering from PTSD: Do or don't? a qualitative study with youth, parents, and clinicians</a>
	<a href="#">Mending invisible wounds: The efficacy and legality of MDMA-assisted psychotherapy in United States' Veterans suffering with post-traumatic stress disorder</a>
	<a href="#">Methylenedioxymethamphetamine (MDMA) in psychiatry: Pros, cons, and suggestions</a>
	<a href="#">Novel psychopharmacological therapies for psychiatric disorders: Psilocybin and MDMA</a>
	<a href="#">Pharmacological therapy for post-traumatic stress disorder: A systematic review and meta-analysis of monotherapy, augmentation and head-to-head approaches</a>
	<a href="#">Psilocybin and MDMA for the treatment of trauma-related psychopathology</a>
	<a href="#">Psilocybin-assisted psychotherapy for depression: Emerging research on a psychedelic compound with a rich history</a>
	<a href="#">Psychedelics and psychotherapy: Cognitive-behavioral approaches as default</a>
	<a href="#">Reviewing the potential of psychedelics for the treatment of PTSD</a>
	<a href="#">Special considerations for evaluating psilocybin-facilitated psychotherapy in vulnerable populations</a>
	<a href="#">The efficacy of psychedelic-assisted therapy in managing post-traumatic stress disorder (PTSD): A new frontier?</a>
	<a href="#">The emerging field of psychedelic psychotherapy</a>
	<a href="#">The emerging role of psilocybin and MDMA in the treatment of mental illness</a>
	<a href="#">Therapeutic role of psilocybin and 3,4-methylenedioxymethamphetamine in trauma: A literature review</a>
	<a href="#">Therapeutic use of psilocybin: Practical considerations for dosing and administration</a>

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.

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