

Psychedelic Medicine: A Rapid Review of Therapeutic Applications and Implications for Future Research

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Expert Commentary

The field of psychedelic-assisted therapy has a rapidly growing evidence base, providing patients, clinicians and health system leaders with promise that this healing approach will soon provide new effective and approved options for a range of mental health and substance use health issues. To help make sense of where the evidence base for these therapies stands in 2022, the writing team has undertaken a rapid but comprehensive review of the current academic literature on psychedelic medicine and science. Their report provides an up-to-date summary of the contemporary clinical research on the most promising psychedelic compounds (including psilocybin, LSD, DMT, MDMA, ibogaine and ketamine) and the various mental illnesses for which evidence of potential treatment efficacy is emerging. Further, and unlike many academic reviews, it also considers findings from traditional indigenous and ceremonial practices and sacred plants such as peyote and ayahuasca within its purview, embracing the transcendent and spiritual domains of healing that have long been alienated within modern medicine. And it also moves beyond just healing or treatment potential of psychedelic substances and delves into the intriguing possibilities of health and well-being promotion, cognitive enhancement and catalysis of creativity that is embedded in the etymology of the term psychedelic itself.

A wide range of potential audiences may benefit from this review, as it provides a helpful summary of the basic pharmacology and neuroscience behind psychedelic-type substances, clinical practice approaches, research methods and limitations, clinical outcomes and naturalistic use findings, and implications for public policy and health system planning. Research scientists and students from a range of disciplines will find it provides a handy and systematically organized reference text for sourcing information on the state of psychedelic science and key foundational bibliographic citations; they will also get a sense of where the current research gaps lie and what kinds of studies might be pursued to fill them. People seeking information about potential research participation or future treatment options for themselves or loved ones may find valuable information about both demonstrated benefits and potential risks, allowing them to consider whether one or another medication or approach may be suitable for learning more about. Health professionals will find summaries of emerging clinical approaches, medication indications and dosing, and adjunctive psychotherapeutic supports, which may be helpful in considering where to take their continuing education pursuits and engaging professional regulatory bodies. Policy makers are provided a thoughtful analysis of the implications of a burgeoning field of knowledge that may provide both opportunities and challenges for (re)designing health system structures to efficiently and equitably deliver these kinds of therapies, if and when regulatory approvals occur.

While the 200+ page report may be lengthy, it is likely most readers will not want to approach the text as one to read from start to finish, but rather as one that provides a number of entry points to dive in and draw from based on particular interests, needs and inclinations. It will offer those who are looking for an overview of the variety of scientific studies and findings on psychedelics a broad scope to survey; for those who may be interested in deeper explorations of particular medications or modalities, they will get an initial bearing on where to go next in the

growing field of peer-reviewed publications on psychedelic science. The writing is clear and succinct and will not burden readers who don't have specialized knowledge from particular disciplines to draw on. In sum, this literature review offers a valuable synthesis of knowledge from the past few decades of research on psychedelic-assisted therapies, and is sure to be a go-to resource for various professionals, policy-makers, students and lay people seeking a credible and comprehensive summary of one of the most exciting areas of medical science today.

Dr. Ken Tupper, July 27th, 2022

Adjunct Professor, School of Population and Public Health, University of British Columbia

1.0 Background and Objectives

1.1 Historical and Current Canadian Context

“Psychedelics” refers to a class of drugs that produce “non-ordinary states of consciousness” and change our sense of self and the world. So-called ‘classic psychedelics’ act as agonists of the 5-HT_{2A} receptor and include lysergic acid diethylamide (LSD), N, N-dimethyltryptamine (DMT), psilocybin, and mescaline. They are also noteworthy for their appearance in many natural fungi and plants used for millennia in healing rituals in many parts of the world. Such naturally derived substances have been referred to as ‘entheogens’ (Ruck et al., 1979), since their intended use is to stimulate a connection with spirits, the Spirit, or some numinous process. Well-known examples of the ritual use of entheogens are peyote/hikuri in Mexico and the US, psilocybe mushroom ceremonies in Mexico, and ayahuasca/yagé in several traditions in South America, among various other psychoactive substances throughout the world. Entheogens may be used in ritual-ceremonial contexts, recreationally, for personal exploration, or in a hybrid social-spiritual manner. Other substances that are also generally considered in the psychedelic class (but are not ‘classic’ psychedelics) include methylenedioxymethamphetamine (MDMA), ketamine, ibogaine and a few others, all acting through somewhat different mechanisms but sharing many of the consciousness-altering effects. Such substances are referred to as ‘atypical psychedelics’, since they stimulate a phenomenologically similar experience to classic psychedelics yet have distinct pharmacodynamics. Psychedelic-assisted treatment aims to harness these effects to address the distress, thought patterns, and neurobiological and behavioural patterns underlying mental health and substance use disorders as well as other health conditions such as chronic pain.

Research on psychedelics as a therapeutic aid has a provocative history dating back to early uses of mescaline in the 1920s, followed by the discovery of LSD in the 1940s. Psychedelics showed great promise as psychotherapeutic aids in the 1950s and 60s, but both methodological and political issues disrupted the once-flourishing domain of inquiry. Amidst growing medico-therapeutic interest in psychedelics, the socio-political factors of the 1960s and 70s driven by racist policy and political persecution led to these drugs being declared illegal, including in Canada, despite a lack of evidence for toxicity or addictive potential. Their designation as Schedule I substances under the UN Convention on Psychotropic Substances, and consequently within the Canadian Controlled Drugs and Substances Act and meant that they were considered as having a high potential for non-medical use¹, no currently accepted therapeutic application, and a lack of accepted safety for use under medical supervision. While this is widely thought to have effectively shut down ongoing clinical studies, psychedelic research did not come to a screeching halt. In addition to the Controlled Drugs and Substances

¹ It is worth noting that non-medical use is often considered synonymous with ‘abuse’ or ‘misuse’ in popular political and health discourses. The concepts of ‘abuse’ and ‘misuse’ are pseudoscientific and unfortunately associated with moralizing and stigmatizing social values, thus in this report we prefer to distinguish between ‘use’, ‘substance use disorder’, ‘problematic substance use’, and ‘non-medical use’.

Act came new regulatory standards for methodological and ethical rigor, which created roadblocks for researchers when clinical trials, and particularly randomized double-blind clinical trials, became the gold standard for proving efficacy (Oram, 2014). The thousands of previous trials largely did not meet the criteria for an adequate and well-controlled study, which meant that funding agencies had little to show for their investments and there was still a pressing need for basic science, safety and efficacy research (Bonson, 2018). Researchers struggled to provide a strong body of evidence for the efficacy of psychedelic-assisted psychotherapy, since the complexity of psychotherapeutic interventions mixed with psychedelics were not easily passed through the RCT model. Further, legal changes made accessing research-grade LSD and psilocybin much more difficult both financially and bureaucratically (Bonson, 2018). Thus, the combination of the socio-political climate, shrinking funding opportunities, and methodological issues have severely limited new research and development since the 1970s (Nutt et al., 2013).

The history and the social-legal convergences that led to the virtual abandonment of this work have been traced by scholars of medicine and science, both inside and outside the field of psychedelics (e.g., Belouin & Henningfield, 2018; Bonson 2018; Harrington, 2019; Mangini, 1998; Langlitz, 2012a; Oram 2014). Popular writers have also contributed to the mainstream discourse on psychedelic use (e.g., Pollan, 2018; Jay, 2019). Before the rapid restriction of this work after the mid-1960s century, some 1000 scientific papers, several dozen books and six international conferences had been documented, as well as treatment prescribed to over 60,000 patients (Drug Enforcement Administration, 1965, as cited in Belouin & Henningfield, 2018). At the end of this prolific period there remained a robust discussion about the sufficiency of the overall scientific body of knowledge regarding treatment efficacy according to prevailing standards of evidence, which were also evolving during the same period, as mentioned above. Within this trajectory, the experimental treatment of substance use disorders was primarily but not exclusively focused on LSD and “alcoholism”, work traced in detail by Mangini (1998) and Dyck (2008). Outside of the US, this includes important work by clinicians and researchers in Europe (Johnstad, 2020) as well as Canada, primarily in Saskatchewan. Work was also undertaken at one of the predecessors to what is now the Centre for Addiction and Mental Health (CAMH) - the Addiction Research Foundation (ARF; Rehm et al., 2010). The work at the ARF had a major influence on US policy and regulatory change related to therapeutic use of psychedelics (see Smart & Storm, 1964; Smart et al., 1966; Smart & Bateman, 1967; also cited in Belouin & Henningfield, 2018).

The past 15 years has seen a rapid resurgence of work in both basic and clinical psychedelic science, with the majority of the work focused on substance use, mental health and related conditions. A wide range of topics are being covered within the domains of neuroscience and psychopharmacology; treatment effectiveness with associated mechanisms of action and safety considerations; palliative, end-of-life, and spiritual care; treatment guidelines; training and certification of therapists and other practitioners; health policy and prevention; as well as anthropology, sociology, and global health. Individual researchers and research centers in the US, Canada, the UK, Brazil, France, and other countries are currently conducting clinical trials to test treatment efficacy with most attention being given to ketamine, MDMA, and psilocybin for mental disorders such as PTSD, depressive disorders, and substance use disorders, including

alcohol and opioid use disorder. This work is being complemented by a wider range of research methods, including observational studies in naturalistic settings; mixed methods; case studies focused on novel treatments and sub-populations; and retrospective accounts of users of psychedelics, including those involved in research and healthy members of the community.

Due to recent changes in the social and political climate concerning psychedelics, researchers have begun to receive special exemptions, regulatory approvals, ethics approvals, and grant funding to obtain and study these substances at a scale not seen in decades, leading to a rise in research outputs, investment in research centres, venture capital investments, government task forces, and stakeholder networks and conferences. Annual publication rates increased dramatically between 2010-2020, marking an all-time high in 2020 (Lawrence et al., 2021), which has likely been surpassed in the following years.

Recent developments of note include the following:

- Papers have been published in high impact journals (e.g., Science; Nature; Cell; Lancet; Neuropharmacology; Psychopharmacology; Canadian Medical Association Journal; British Journal of Psychiatry; British Medical Journal; Drug and Alcohol Dependence, to name just a few).
- Psychedelic research has been represented in major international addictions-focused conferences (e.g., CPDD 2018 <https://cpdd.org/wp-content/uploads/2018/06/2018-CME-Approved-Sessions.pdf>); Lisbon Addictions, 2019 <https://www.lisbonaddictions.eu/lisbon-addictions-2019/keywords/psychedelics> and will be well-represented again at the same conference in November 2022.
- A wide variety of psychedelic science-focused conferences (e.g., Psychedelic Science hosted by MAPS and the Beckley Foundation, in 2013, 2017, and forthcoming in 2023 <https://2017.psychedelicscience.org/videos>); International Society for Research on Psychedelics: Inaugural Conference, October, 2019 <http://www.isrpsych.org/>; and several smaller workshops and dedicated research-oriented events in the US and Canada (e.g., University of Ottawa workshop on Transcendence: Psychedelics and Spiritual Healing at the End of Life, December 2018) https://arts.uottawa.ca/cla-srs/sites/arts.uottawa.ca/cla-srs/files/csps.psychedelics.programme.speakers.final_.pdf.
- Major Canadian conferences have included: the Canadian Biomarker Integration Network on Depression (CAN-BIND) conference in October 2021 “Psychedelics in Canada: Now and in the Future”, that engaged over 500 participants (<https://www.canbind.ca/psychedelicscanada/>); Catalyst Summit 2022: Psychedelic Medicine Global Conference and 2023 <https://www.catalystpresents.ca/>; and the in-person conference in Toronto in May 27-29, 2022 entitled “From Research to Reality: Global Summit on Psychedelic-Assisted Therapies and Medicine” co-sponsored by the Centre for Addiction and Mental Health, the Canadian Centre on Substance Use and Addiction, and the Mental Health Commission of Canada <https://fromresearchtoreality.com/>. Pre-conference R2R webinars supported by the planning committee and CAMH knowledge exchange resources were held, the first attracting 538 registrations.

- In the US context, the American Psychological Association has featured panels on psychedelic-assisted therapy <https://chacruna.net/psychedelics-panel-invited-to-mainstream-healthcare-conference/> and leading academic health science institutions have been developing new centres on psychedelic-assisted medicine and hosting webinars aimed at a broad research audience (e.g., <https://www.massgeneral.org/psychiatry/treatments-and-services/center-for-the-neuroscience-of-psychedelics>). Further, in January 2022, the National Institute of Mental Health, the National Institute on Drug Abuse and the National Institute on Alcohol and Alcoholism co-sponsored a two-day NIH workshop ‘Psychedelics as Therapeutics: Gaps, Challenges, and Opportunities’ (<https://www.nimh.nih.gov/news/events/2022/psychedelics-as-therapeutics-gaps-challenges-and-opportunities>).
- Recent grants and philanthropic donations have made dedicated psychedelic research centres possible at Johns Hopkins University, Harvard University, University of California, San Francisco (UCSF), and University of California, Berkeley (UCB) in the US, and Imperial College London in the UK. In Canada, formal centres have been established at Queen’s University, The University of Ottawa, and the Nikean Psychedelic Psychotherapy Research Centre hosted by the University Health Network in Toronto. Active foci of work also include the University of Toronto, the Centre for Addiction and Mental Health (CAMH), McGill University, and University of Alberta, to name just a few “hot spots” of Canadian research and development.
- The University of Ottawa has welcomed a new Canada Research Chair for Mental Health Disparities (Dr. Monnica Williams) whose work is focused on equitable access to psychedelic-assisted treatments, and who has developed a formal University of Ottawa study curriculum focused on psychedelic science.
- Networks and networking opportunities have been established in Canada to bring key stakeholders together to share information and encourage collaboration. This includes the Canadian Psychedelic Association (<https://www.psychedelicassociation.net/>) and the nascent Canadian Psychedelic Research and Policy Network, inclusive of researchers from across Canada as well as key policy makers (e.g., Health Canada). A Canadian Psychedelic Research Collaborative has also formed to foster collaboration and multi-site projects in the Canadian context.
- Recently, Chao & Horton (2021) on behalf of CADTH², an independent, not-for-profit organization responsible for providing Canada’s health care decision-makers with research to support evidence-based decision-making, undertook a rapid health technology review on psychedelic-assisted psychotherapy, focusing on PTSD, as well as anxiety, mood, and substance use disorders.

² CADTH Health Technology Review (2021)

- To date, there have been over 50 approvals by Health Canada for exemptions to use psilocybin for health/mental health reasons, primarily for end-of-life distress, largely due to the advocacy work of TheraPsil, a B.C.-based non-profit organization.
- In January 2022, the Canadian government altered the Special Access Program (SAP) to allow healthcare professionals to request psilocybin on behalf of their patients for emergency use.
- Health Canada has granted a total of six exemptions for the importation and use of ayahuasca in the context of the Santo Daime and União do Vegetal (UDV) religious practices. This religious-use context that has been fruitful ground for many years of both naturalistic study and basic science concerning the therapeutic potential of ayahuasca in a ritual setting, as well as important safety considerations.
- In Oregon USA, Measure 109 was passed in 2020 to regulate the use of psilocybin (Oregon Measure 110 descriminalized all drugs up to specific quantities). An advisory board to the Oregon Health Authority recently conducted a rapid evidence review³ on the therapeutic efficacy of psilocybin as part of its process to establish the state-level psilocybin services framework.
- A wide variety of training initiatives are now underway, including the well-known Certificate in Psychedelic-Assisted Therapies and Research offered by the California Institute for Integral Studies (CIIS) Center for Psychedelic Therapies and Research. The Icahn School of Medicine at Mt. Sinai in New York City is also now offering education/training for clinicians (<https://icahn.mssm.edu/research/center-psychedelic-psychotherapy-trauma-research/training-education>).
- In the Canadian context, the University of Toronto Certificate in Psychedelic-assisted Psychotherapy has been established by the Nikean Psychedelic Psychotherapy Research Centre at the University Health Network (UHN) in Toronto. The program was developed in partnership with the Michener Institute at the University of Toronto and with the California Institute of Integral Studies and the first course began in September 2022 with 17 participants. The NResearch Centre also hosted an on-line Psychedelic-Assisted Psychotherapy Conference in May 2022.
- The University of Ottawa is now offering Canada's first microprogram in Psychedelics and Spirituality Studies with the goal of offering students a pathway to completing a Ph.D. in Psychedelic Studies.
- The Psychedelic-assisted Therapy Certificate Program at Vancouver Island University was initiated in the Fall of 2022 (<https://hhs.viu.ca/psychedelic-assisted-therapy>).
- In early March 2022, the Canadian Institutes of Health Research (CIHR) pre-announced the launch of the Operating Grant: Psilocybin-assisted Psychotherapy for Mental Health and Substance Use Disorders funding opportunity. This funding opportunity is led by

³ The Oregon Psilocybin Evidence Review Writing Group (2021)

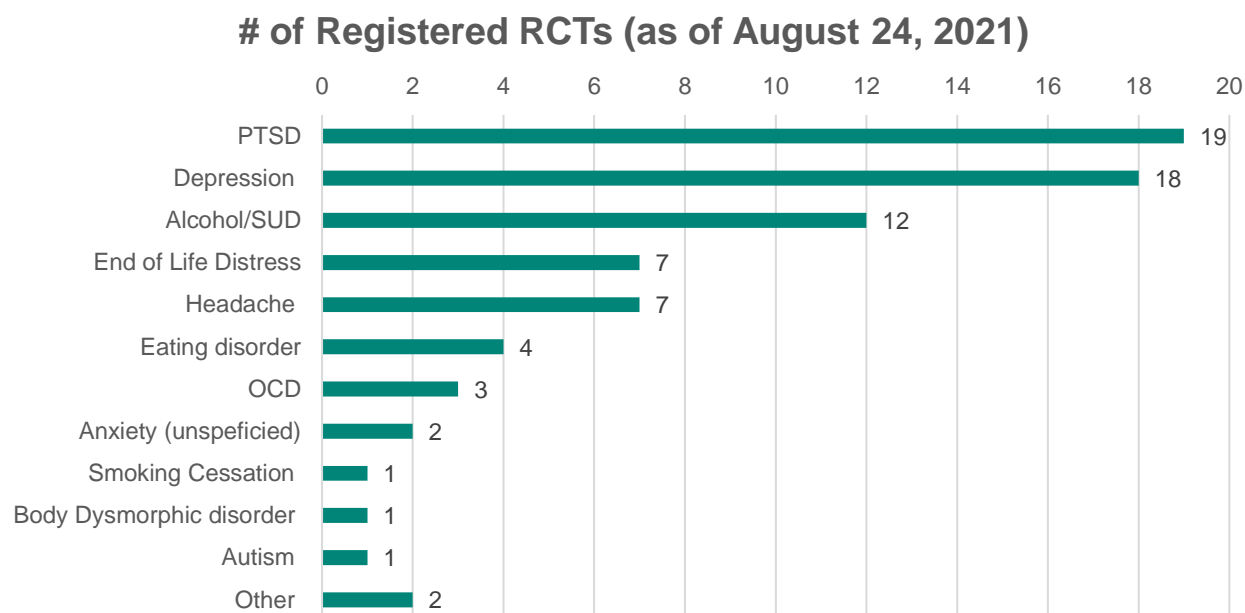
CIHR's Institute of Neurosciences, Mental Health and Addiction (INMHA) with funding provided by the Canadian Drugs and Substances Strategy (CDSS). The focus of the operating grant is to support Phase 1 or 2 clinical trial research into the safety and early efficacy of using psilocybin, in combination with psychotherapy, to treat substance use and mental health disorders.

- In July 2022, CAMH was awarded Canada's first federal grant to study psilocybin with regard to its effect on treatment-resistant depression.
- Several Canada-based venture capital start-ups to develop, promote, and market psychedelic-assisted therapy have been initiated (e.g., Numinus, Revive Therapeutics, Filament, Field Trip Health, and Dimensions Health Centers, to name just a few). A new non-profit trade association, Psychedelics Canada, has recently been created with goals to advance the regulatory landscape and advocate on behalf of the wide range of stakeholders in the psychedelic industry. Relatedly, the stock market is rife with speculation, reminiscent of the halcyon days of the early cannabis-related market.

1.2 Current Clinical Trials Investigating Psychedelics

In order to gauge the extent of current clinical trial activity where trials are ongoing but have not yet published results, we conducted a search of the clinicaltrials.gov database to find current clinical trials (2014-2023) investigating psychedelics. The search was performed by inputting the name of various psychedelic medicines (psilocybin, MDMA, LSD, ayahuasca, iboga/ibogaine, and DMT/5-MeO-DMT), but excluded ketamine due to the large number of trials. Clinical trials investigating the efficacy and safety of psychedelics in the treatment of mental and substance use disorders were included. Studies investigating pharmacodynamics, pharmacokinetics, mechanisms of action, and effects in healthy volunteers were excluded as they lacked a clinical application. At the time of data extraction (August 24, 2021), a total of 77 clinical trials were identified (see Appendix 1) involving 2809 participants currently underway internationally. 45 trials investigate psilocybin, and 24 focus on MDMA. LSD, ibogaine, DMT and ayahuasca also feature prominently, with trials designed for a wide range of mental health as well as neurological conditions. Figure 1 shows the number and distribution of these trials according to the mental health and substance use health condition. Of the clinical trials included, 22% were registered, 53% were in process, and 25% were completed. No clinical trials investigating mescaline were identified in our search. Two trials are listed that investigate the acute effects of mescaline, but not specifically its therapeutic use, therefore these were excluded from consideration. Although the authors are not aware of any existing clinical trials that investigate the therapeutic use of mescaline (or peyote and *huachuma*), it is worth noting that the biopharmaceutical company Journey Colab claimed they would conduct clinical trials in 2022 with synthetic mescaline hydrochloride for alcohol use disorder (<https://www.journeycolab.com/>). 1,099 current clinical trials investigating ketamine were found in our search, not all of which were focused on therapeutics with respect to mental health and substance use.

FIGURE 1. STATUS OF CLINICAL RESEARCH AT TIME OF SEARCH BY HEALTH CONDITION



A similar summary of registered clinical studies investigating psychedelic drugs for psychiatric disorders was conducted by Siegel and colleagues in July of 2021 (Siegel et al., 2021). They found the majority of registered studies aimed to investigate MDMA (46%) and psilocybin (41%) somewhat similar to the priorities in our recent search. However, our search indicated that interest seems to have shifted towards psilocybin (58%) rather than MDMA (31%). Other psychedelics being investigated were LSD (4%), ibogaine (3%), DMT (3%), and ayahuasca (1%). These clinical studies focused on a range of mental disorders. 12 studies investigated substance use disorders, with seven specifically focused on alcohol use disorder and one focusing on smoking/nicotine cessation. 18 studies were focused on depression, with seven specifically focusing on major depression; five on general depression; five on treatment-resistant depression (TRD); and one on depression and anxiety related to Parkinson's disease. Five studies were investigating eating disorders (ED), with three focusing specifically on anorexia nervosa and one focusing specifically on body dysmorphic disorder (BDD). 23 studies were investigating anxiety disorders, with one study focusing specifically on generalized anxiety disorder, three focusing on obsessive-compulsive disorder (OCD), and 19 focusing on post-traumatic stress disorder (PTSD). Seven studies were focusing on headaches. Autism spectrum disorder, bipolar disorder, demoralization among long-term HIV/AIDS survivors, and diabetes insipidus were also being researched at the time of the search.

Clearly the scope of work and interest underway in the domains of mental health, substance use research and development and knowledge translation is quite broad and growing rapidly. This raises several questions of high interest for a host of stakeholders, including but not limited to: researchers and their funding bodies and regulators; decision-makers in the national, provincial, and territorial health policy arenas; professional societies across a breadth of health and social

service practitioners; Indigenous leaders, elders, and their communities; and the Canadian public at large.

We embarked on a broad but rapid review to synthesize the current state of knowledge in this rapidly expanding body of work with a view to identifying research gaps as well as opportunities in the Canadian context. We begin here with a brief overview of the history and emergence of this area of research and practice, followed by a summary of the Canadian context, touching briefly on international trends and current issues. Following the description of our methodology and articulation of scope, we provide an overview of the psychoactive substances of primary concern (e.g., MDMA, psilocybin, LSD, ketamine), mechanisms of action and “typical” treatment protocols. Our intention in doing so is to educate relatively naïve stakeholders about “the basics,” with the primary focus on the literature concerning clinical effectiveness. As such our coverage of basic mechanisms and details of various models or protocols for delivery of psychedelic-assisted treatment is meant simply to help orient the readership to those parts of particular relevance to the treatment outcome research. We conclude our assessment of the evidence concerning treatment effectiveness with a brief overview of other considerations for research in this area, including research methodology and study design, safety, representation of research populations, regulation and policy, credentialing, issues related to Indigenous populations, and also the role of psychedelics in overall population health and wellness. To conclude we offer our perspective on some research gaps and provide a framework to support further discussion and prioritization among key stakeholders.

While our focus here is on implications for research, and primarily research in the Canadian context, we anticipate that further review, refinement and focus of the research summary contained herein will contribute to areas of interest among a wide variety of stakeholders. Looking ahead, we also recommend regular updates to this research summary and development of more concise knowledge translation products suitable for multiple audiences.

1.3 Statement of Objectives

- To summarize the extant body of research on the effectiveness of psychedelic substances for the treatment and support of people experiencing mental and substance use disorders and other related health conditions;
- To provide an overview of issues and considerations relevant to research and development in this area, including the need for large clinical trials as well as diversity in methods and study participants;
- To highlight gaps in knowledge and opportunities for research investment in the Canadian context.

2.0 Methods

2.1 Search Process and Terms

We undertook a rapid review using a highly structured search string of key words and phrases in several iterations to focus on the references of most relevance to the project objectives. The time frame of potential material to be selected was 1990 to 2021. Languages included English, French, Spanish and Portuguese. After completion of the initial review in July 2021, the team continued to identify additional studies published through August 2022, which were hand-sorted for inclusion and reference in this rapid review. Search terms are listed in Table 1, databases searched included CINAHL, Web of Science, OVID (AMED, Embase, MEDLINE/ PubMed, PsycInfo), and Proquest (ERIC, PsycArticles).

Based on our initial search we obtained 52,293 references. Upon review it was determined that a small number of terms such as LSD⁴ and DMT⁵, as well as certain terms such as “public policy”, “therapist”, and “credentialing” were yielding a significant amount of out-of-scope material. A revised search string then yielded 23,371 results, of which 12,009 were duplicates (see Figure 2). Using Covidence software, two analysts then shared the task of reviewing the full set of titles and abstracts (when available) and separating the list into studies based on research on humans versus animal models, clinical trials, or other outcome-focused research relevant to study objectives; for example, papers on safety and adverse events, historical reviews, and commentary. The analysis excluded work focused specifically on animal models, neuroscience, and psychopharmacological mechanisms, although some individual studies and reviews clearly touch on both foundational mechanisms and clinical therapeutics. The specific inclusion and exclusion criteria are listed below.

This result was 1717 citations which were then transferred to an Excel file for ease of sorting and further review. All were in English. During a categorization process by one of the team analysts, a further 103 citations were judged to be out-of-scope, leaving 1613 articles for further review of titles and abstracts. One senior team member (BR) then reviewed all citations and highlighted those of primary interest and within scope. The focus at this stage was on selecting:

- Narrative, scoping or systematic reviews published since 1990;
- Clinical trials, observational studies, and case reports published in the last three years (2018-2020); and
- Papers devoted to the following sub-topics: historical reviews and expert commentary, regulatory consideration, research methods, participant representation, and risk assessment, including safety and adverse events.

⁴ Least Significant Difference

⁵ Dance Movement Therapy

TABLE 1. COVIDENCE SEARCH STRATEGY

Psychedelics/Hallucinogens	Mental Health/Substance Use Disorders ⁶ and End of Life
1. Hallucinogens/ad, hi, pk, pd, tu [Administration & Dosage, History, Pharmacokinetics, Pharmacology, Therapeutic Use]	14. exp Mental Disorders/
2. psychedelic*.mp.	15. exp "Tobacco Use Cessation"/
3. MDMA.mp.	16. exp Grief/
4. Ketamine/ad, bi, hi, pk, pd, tu [Administration & Dosage, Biosynthesis, History, Pharmacokinetics, Pharmacology, Therapeutic Use]	17. exp Palliative Care/ or exp Terminally Ill/ or exp Terminal Care/
5. DMT.mp.	
6. Methoxydimethyltryptamines/ad, bi, hi, pk, pd, tu [Administration & Dosage, Biosynthesis, History, Pharmacokinetics, Pharmacology, Therapeutic Use]	
7. 5-MeO-DMT.mp.	
8. peyote.mp.	
9. Psychomimetic.mp	
10. entactogen.mp.	
11. entheogen.mp.	
12. iboga.mp. or exp Tabernaemontana/	

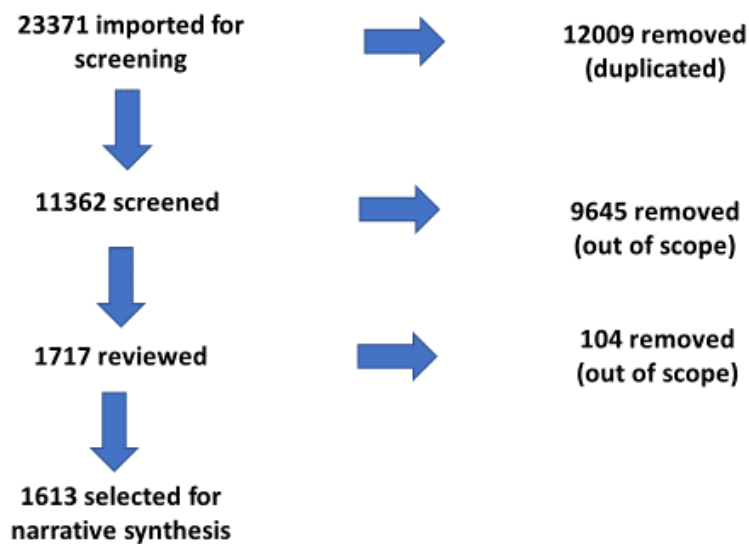
This process resulted in 1613 studies which were selected for further in-depth review by the review team, and which forms the foundation of our assessment of treatment effectiveness and related topics. During this last stage of culling relevant papers, the team identified other articles, book chapters, and reviews that focused on historical trends, safety, research design, policy, and regulation for narrative purposes on these sub-topics. These papers were downloaded and made available to all team members through a shared folder on Dropbox. The current holdings of relevant publications among the project team as well as the reference list of key review papers were also examined for additional relevant material. During the final stages of report editing and preparation, team members continued to identify and share recently published grey-literature reports, as well as several papers recently published up until August 2022. The review team hand-sorted additional publications that were considered relevant for keeping the report up to date throughout the editorial process.

In the end, our process was guided by the resources and time frame available for the review and synthesis and is best characterized as a **rapid review** rather than a systematic or scoping review. Rapid reviews are a kind of knowledge synthesis in which components of a systematic review process are simplified or omitted to produce information in a short period of time, often to give health decision-makers timely access to information upon which to base decisions (Tricco et al., 2015). Time and resources did not allow for two independent reviewers of the output from the search process to filter for the most relevant material with an established set of criteria, nor

⁶ Behavioural addictions such as Internet Gaming Disorder and Gambling Use Disorder were not included

for a formalized and structured data extraction process from the retrieved papers. Based upon a draft Table of Contents and division of labour, the team members each took responsibility for a topic area organized by health condition (e.g., substance use disorders, depressive disorders, PTSD) and drafted the initial material for subsequent review and suggested revisions by all team members. Similarly, team members also variously took the lead on additional sub-sections such as safety, the Indigenous lens, population health and wellness. All team members contributed to the articulation of research gaps and opportunities in the Canadian context.

FIGURE 2. SEARCH STRATEGY RESULTS



2.2 Scope

Inclusion Criteria

The following health conditions were considered in scope:

- Substance Use Disorders
- Depressive Disorders
- Anxiety Disorders including PTSD
- End-of-Life Distress
- Eating Disorders and Body Dysmorphic Disorders
- Outcomes related to headache and pain
- Other health and mental health-related conditions including
 - Autism Spectrum Disorder
 - Personality Disorders

- Schizophrenia
- Grief
- Alzheimer's, Dementia, and Neurocognitive Disorders
- Traumatic Brain Injury
- Well-being, Cognition, Mindfulness, and Creativity

Where relevant for specific research topics we also include reference to co-morbidities, for example, depressive disorders and alcohol use disorders, while noting that we did not search and extract all details specific to this important topic.

As noted earlier we limited our scope to the following psychedelic substances:

- Psilocybin
- LSD
- Ketamine
- Ayahuasca
- DMT and 5-Meo-DMT
- Mescaline/peyote
- MDMA
- Iboga and ibogaine

Also noted earlier is our focus on research emanating from clinical trials and observational/naturalistic studies assessing health and wellness outcomes in the areas identified above as well as recent and atypical case reports. We aimed for studies in English, French, Spanish, and Portuguese, although all abstracts were returned and reviewed in English.

Populations of interest included adults, the focus of almost all the research, as well as adolescents when noted by title or abstract. Analysts paid particular attention to issues noted in the title or abstract related to gender, diversity, and equity issues to be summarized in the section on research methods and challenges (Section 6.2.3). Similarly, we were attentive to Indigenous-related issues and commentary while drawing primarily upon team experience and their current research holdings in this area.

Exclusion Criteria

Appendix 2 contains an exhaustive list of all substances considered in the 'psychedelic' class. Based on this list our **exclusions** were: phencyclidine (PCP), cannabis, scopolamine, the 2-C and DOx families of novel psychedelic compounds, Salvia divinorum, fly agaric mushrooms, NBOMe derivatives, alpha-methyltryptamine (α MT), and tobacco/nicotine. While these compounds may be considered psychedelic or are used in entheogenic rituals to achieve

altered states of consciousness, their inclusion was considered outside the scope of the review objectives and their focus on research concerning treatment effectiveness.

We also excluded work in the areas of anthropology and medical sociology, traditional and complementary medicine, and religious studies except insofar as drawing links between clinical outcome-focused research and issues related to an Indigenous cultural lens on healing, traditional medicine and sacred plants. As noted earlier, we also excluded papers focused solely on neuroscience and psychopharmacology except insofar as to provide the reader with a basic discussion of mechanisms postulated to underly treatment effectiveness. Lastly, we did not aim for inclusion of works specifically related to prevention and health promotion at the population level, although the review process turned up excellent material related to psychedelic use and population health and wellness, as well as sufficient material to engage the reader in the importance of public health and public health policy as they relate to expanded therapeutic and research opportunities in this area.

3.0 Overview of Psychedelic Substances

3.1 Defining Psychedelics

Psychedelics are categorized by their shared subjective experience of a significantly altered state of consciousness with profound capacity to reliably induce shifts in perception, cognition, and mood (Calvey & Howells, 2018). Though originating in diverse chemical families, various compounds that are classed as psychedelics typically demonstrate cross-tolerance, produce markedly similar effects in both animals and humans, and are understood to have common metabolic pathways, effecting common anatomical regions of the brain (Halberstadt, 2015). Psychedelics share discriminative stimulative effects and selective agonism of serotonin-1 (5-HT₁) and serotonin-2 (5-HT₂) receptor subtypes. Classic psychedelics stimulate dopamine via D2 receptors and indirectly stimulate glutaminergic and GABAergic (gamma-aminobutyric acid) systems (Nichols, 2018). Classic psychedelics commonly stimulate 5HT_{2A} cortical layer V pyramidal neurons, triggering disruptive signalling pathways and cortical desynchronization across various key brain regions, creating a time-limited state of entropy, and allowing for the loosening of rigid neurological and cognitive patterns (Carhart-Harris, 2016; Muthukumaraswamy et al., 2013; Rucker et al., 2018).

In brief, psychedelics can be understood by: “(1) their pharmacodynamics and molecular structure; (2) the subjective perceptual, psychological, and/or spiritual effect;” and (3) the source material from which the compounds are derived, extracted or synthesized (Lawrence & Carhart-Harris, 2019).

Psychedelics are divided into classic and non-classic, or atypical. Classic psychedelics include two structural types: indoleamines (lysergic acid diethylamide or LSD, dimethyltryptamine or DMT, and psilocybin from *Psilocybe* mushrooms) and phenylalkylamines (mescaline from peyote and modern synthetics such as the 2C-X family). Additional atypicals include dissociatives such as ketamine, entactogens such as MDMA, and the NMDA agonist and tryptamine ibogaine (Calvey & Howells, 2018; Halberstadt et al., 2017; Nichols, 2018; Sellers et al., 2018).

For purposes of this overview on treatment effectiveness, the extant literature supports grouping these various compounds together into a unitary class of psychedelic drugs. However, much of how psychedelics produce their tell-tale effects remains unknown, while data on serotonin affinity and functional potency are not available for many compounds. Further we reiterate the importance of the broad categorization of naturally derived entheogenic psychoactive substances used in ritualistic/spiritual context. These are represented primarily but not exclusively within the classic psychedelic grouping above (e.g., peyote, San Pedro/huachuma, ayahuasca, *Psilocybe* mushrooms).

3.2 Psilocybin

Psilocybin (4-phosphoryloxy-*N*, *N*-dimethyltryptamine) is a naturally-occurring tryptamine indolealkylamine and a prodrug to psilocin (4-Hydroxy-*N*,*N*-dimethyltryptamine), a central serotonin 5HT_{2A} receptor agonist. Along with lysergic acid diethylamide (LSD) and *N*, *N*-dimethyltryptamine (DMT), psilocybin is considered a classic serotonergic psychedelic. First isolated and identified in 1958 by Albert Hoffman from the fungal species *Psilocybe mexicana*, psilocybin is the main psychoactive molecule found in close to 300 species of psychoactive mushrooms (Guzmán, 2005). Sacramental use of the *Psilocybe* genus of gilled fungi in Mesoamerica has been dated to 500 BC (Guerra-Doce, 2015), with shamanic ceremonial healing traditions documented among many Indigenous populations throughout central and southern Mexico, as well as among the Yurimagua of Peru (Schultes & Raffauf 1993, Guzmán, 2008, McKenna & Riba, 2016). Psilocybin-containing mushrooms are globally distributed (Guzmán et al., 1998) and evidence suggests their ancient ritual use in Africa and Europe (Froese et al., 2016).

Onset of action for psilocybin is 20-40 minutes after oral ingestion, with peak levels experienced after 60–90 minutes, and overall duration of effect is 4–6 hours (Hasler et al., 1997; Passie et al., 2002). Psilocin is largely excreted after 3 hours, and completely eliminated after 24, with a half-life of 2.5 hours (Tylš et al., 2014). Psilocybin produces biphasic effects of both stimulation and inhibition. Peak effects on emotional excitability and sensitivity, heightened mood, and concentration occur in the early phase of drug metabolism (60-180 min). Effects such as dreaminess, dazed state, inactivation, and introversion are more pronounced in later stages (260-400 min; Hasler et al., 1997; Studerus et al., 2011). Subjects tend to be more active, emotional, extroverted, and cognitively impaired in the early stages; derealization and depersonalization take precedence over visual hallucinations approximately 90-120 minutes after drug intake (Studerus et al., 2011). Psilocybin has a very high safety ratio and a low risk profile (Gable, 2004) even in unsupervised, naturalistic settings (Schenberg, 2018; Nutt et al., 2010).

While psilocybin is biologically safe and relatively non-toxic compared to other psychoactive compounds (Amsterdam et al., 2011; Carbonaro et al., 2016; Gable, 2004), it has been associated with psychological distress, erratic behavior, and a small possibility of harmful behavior while under drug effect (Johnson et al., 2008; Rucker et al., 2016; Sellers et al., 2018; Studerus et al., 2011). Psilocybin increases blood pressure and heart rate and may result in transient hypertension, tachyarrhythmias and hyperthermia (Passie et al., 2002). Other possible side effects include nausea, vomiting, acute and delayed headaches, dizziness, paresthesia, blurred vision, dilated pupils, and increased tendon reflex (Johnson et al., 2008; Sellers & Leiderman, 2018; Studerus et al., 2011).

Serotonin (5-hydroxytryptamine, or 5-HT) receptors regulate a range of biological processes including learning and memory, sleep and wake cycles, thermoregulation, appetite, sexual behaviour, pain, motor activity, and aspects of autonomic function (Flanagan & Nichols, 2018). The 5HT_{2A} binding sites (receptors) are expressed in high density across all layers and areas of the neocortex (Nichols & Nichols, 2008). Classical psychedelics are thought to primarily target

5-HT_{2A} receptors, resulting in novel patterns of global neurological connectivity (Carhart-Harris et al., 2012), experiences of entropy (Carhart-Harris et al., 2014), or cortical desynchronization (Muthukumaraswamy et al., 2013). When combined with the appropriate clinical preparation and setting, such agonism of serotonergic receptor sites are hypothesized to result in a subsequent, beneficial “rewiring” of brain networks away from previous pathological patterns and toward states more similar to pre-disease conditions (Carhart-Harris et al., 2017; Nichols et al., 2017) and characterized by positive mood and sustained improvements in mental health (Calvey & Howells, 2018; De Gregorio et al., 2018).

Recent evidence supports this concept of neuronal rewiring as serotonergic psychedelics have been demonstrated to induce neuroplasticity, promote dendritic spine growth, increase dendritic arbor complexity, and stimulate synapse formation (Ly et al., 2018; Savalia et al., 2021). Serotonergic psychedelics have also been shown to promote cell survival, have neuroprotective effects, and modulate the neuroimmune systems of the brain (Calvey & Howells, 2018) while reducing neuroinflammation (Flanagan & Nichols, 2018). Due to these multiple beneficial health effects, the use of serotonergic psychedelics has potential for changing the approach to treatment of mental disorders (Nichols et al., 2017), including substance use disorders (Morgan et al., 2017), neuroinflammation (Flanagan & Nichols, 2018), and mood disorders (Andersen et al., 2021; Brekke et al., 2020).

Several systematic reviews on the clinical application of psilocybin have recently been published (Bahi, 2018; Castro Santos & Gama Marques, 2021; Vargas et al., 2020). Investigations have indicated that the phenotypic expression of the 5-HT_{2A} receptor genotypes is tethered to, and dependent on, environmental context (Jokela et al., 2007), and this sensitivity to setting is integral to the functioning of 5-HT_{2A} signaling (Carhart-Harris & Nutt, 2017). In preclinical studies assessing measures of exploratory and investigative behavior, psilocybin results in reduced locomotor activity and enhanced neophobia in rodents, analogous to the sensitivity to context shown in humans under the influence of psychedelics (Araújo et al., 2015; Carhart-Harris et al., 2018c; Halberstadt et al., 2017). Proponents of psychedelic therapy have long paid heed to the importance of both set — personality, mindset, affect, expectations (Metzner & Leary, 1967) — and setting, or the environmental and social context (Hartogsohn, 2017; Leary et al., 1963). The triad of substance, set and setting is foundational to understanding the total effect of any psychoactive substance (Zinberg, 1984) and central to harm reduction (McElrath & McEvoy, 2002; Shewan et al., 2000). Indeed, some clinical trials are actively incorporating what is known as a Set and Setting (SaS) framework that includes preparation, psychoeducation, and an integration period (Guss et al. 2020).

Several mechanisms of action for psilocybin in the treatment of mood disorders have been proposed. fMRI studies indicate one of psilocybin’s effects is the deactivation of the medial prefrontal cortex (mPFC), a brain hub typically hyperactive in depressed patients (Carhart-Harris et al., 2016a). Psilocybin may also attenuate amygdala activation in response to potentially threatening visual stimuli; amygdala hyperactivity in response to negative stimuli is correlated with negative mood states in depressed patients (Vargas et al., 2020). The anti-inflammatory effects of psilocybin may also be implicated in therapeutic outcomes (Flanagan & Nichols, 2018). Kuypers further speculates that the effects of psilocybin on the microbiome are of benefit

given the preponderance of serotonin in the gut, resulting in improved gastrointestinal function, improved gut-brain communication and self-regulation, while resulting in increased production of neuro-protective molecules (Kuypers, 2019).

The therapeutic potential of *Psilocybe* mushrooms may not be limited to the psilocybin compound alone; psilocin, baeocystin, norbaeocystin, aerguinascine, norpsilocin and phenylethylamines are also found in *Psilocybe* mushrooms and may themselves have value alone or in entourage (Kuypers et al., 2019; Wiczorek et al., 2015). Further, recent investigations have found the presence of beta-Carbolines in *Psilocybe* mushrooms resulting in an ayahuasca-type synergy of psychoactive alkaloids and potent monoamine oxidase inhibitors, which themselves have anti-depressant or mood-boosting effects and potentiate the psychedelic serotonergic effects (Blei et al., 2020).

The promising therapeutic potential of psilocybin-assisted treatment has been summarized by several authors (e.g., Johnson & Griffiths, 2017; Galvão-Coelho et al., 2021). Twelve clinical trials using psilocybin for a variety of health conditions have been completed and results published. Eight of the 12 studies used a controlled trial methodology, and four trials were single-group open label trials lacking control groups. A total of 259 participants completed the trials, with 198 (76%) enrolled in controlled trials and 97 (37.5%) enrolled in trials pertaining to cancer-related anxiety and depression. Other presenting conditions studied include OCD, tobacco and alcohol use disorder, treatment resistant depression, demoralization among long-term AIDS survivors, and migraine headaches. Nine of the trials took place in the United States, and the remaining three in the United Kingdom. The earliest trial for psilocybin-assisted treatment published results in 2006 (Moreno et al., 2006). See Section 4.0 for summaries of the literature on the effectiveness of psilocybin-assisted interventions for various mental and substance use disorders and other health-related conditions.

In 2018, the USA Food and Drug Administration (FDA) designated psilocybin as a “breakthrough therapy” for the treatment of depression. There are currently several Phase 2/3 clinical trials at various sites in the U.S., Canada, and Europe. In 2022, the USA government declared the need to establish a special task force to prepare for the legalization of psilocybin and MDMA by 2024.

3.3 LSD

Lysergic acid diethylamide (LSD), first synthesized in 1938, is a potent chemical and tetracyclic ergoline considered a prototypical psychedelic (Calvey & Howells, 2018; Carhart-Harris et al., 2012; Nichols, 2018). LSD is a semi-synthetic analogue of d-lysergic acid amide (LSA), an ergot-type psychoactive alkaloid found in the seeds of *Ipomoea corymbosa* (aka morning glory), known traditionally as *Ololiúqui* by the Nahuatl peoples of southern Mexico. LSD displays high affinity for 5-HT receptors (Halberstadt, 2015) as well as stereospecific binding to the dopamine (D2) receptor and has partial agonist activity at D-1 type receptors (De Gregorio et al., 2018). Both LSD and psilocybin demonstrate mood-altering properties, perhaps due to their pleiotropic effect on serotonergic (5-HT), dopaminergic (DA) and glutamatergic systems (De Gregorio et al., 2018; López-Giménez & González-Maeso, 2018).

De Gregorio et al. (2018) found that a single dose of LSD increased blood oxygen levels in the prefrontal cortex in response to music, suggesting enhanced personal processing enmeshed with sensory stimuli. LSD has been shown to increase visual cortex cerebral blood flow and resting state functional connectivity (Carhart-Harris et al., 2016b). A MEG study reported that psilocybin, LSD and ketamine all increased signal diversity within occipital cortices, extending over parietal cortex with LSD and over full cortex (but not medial frontal brain) with ketamine (De Gregorio et al., 2018)

LSD reduces resting state functional connectivity of the default-mode network (DMN), which is a major resting state network (RSN) in which increased activity is associated with both depression and schizophrenia and is also correlated with deficits in working memory and attention (Carhart-Harris et al., 2016b). The attenuating effects of psychedelics on the DMN may help explain their purported anti-depressant effects. Genes acutely activated by LSD are predominantly involved in synaptic plasticity. LSD also acts on non-neuronal cells such as glia and astrocytes (Kuypers et al., 2019).

LSD research was robust during the mid-20th century advent of modern psychopharmacology from the 1950s through to the early 1970s in the treatment of various mental disorders, particularly problematic alcohol use. Canadian history in pioneering the use of LSD in the field of psychiatry at the Weyburn Mental Hospital in Saskatchewan and the Hollywood Hospital in British Columbia have been described by historian Erika Dyck (Dyck, 2008). Canadian research was also undertaken at the (then) Addiction Research Foundation in Toronto (Smart & Bateman, 1967; Smart & Storm, 1964; Smart et al., 1966).

Much of the early LSD research is characterized by poor trial design and many carry significant ethical concerns. One recent systematic review analyzed outcomes of 567 patients who were administered LSD in the context of randomized controlled trials (RCTs), with LSD given in doses ranging from 20mcg to 800mcg (Fuentes et al., 2020). Five of eleven trials were found to demonstrate a high risk of bias; two trials had high risk of bias due to incomplete outcome data; four studies had substantial rates of missing participants at follow-up; three showed possible selective outcome reporting; and four had significant high risk of other sources of bias (Fuentes et al., 2020). The review showed that efficacy was highest in trials for alcohol use disorder while other trials demonstrated efficacy in the treatment of neurotic symptoms (anxiety, depression, and psychosomatic disease), opioid use disorder, and anxiety associated with life-threatening disease. Krebs & Johansen (2012) conducted a meta-analysis of the best designed LSD clinical trials for alcoholism in the late 1960s and early 1970s, synthesizing outcomes for 536 participants and substantially improving the evidence for a beneficial effect of LSD on alcohol use disorder. Efficacy in treating alcohol use disorder may be explained by the elicitation of insights into behavioral patterns and enhancement of motivation for change (Dyck, 2008). See Section 4.0 for summaries of the literature on the effectiveness of LSD-assisted interventions for various mental and substance use disorders and other health-related conditions.

A recent systematic review of contemporary research suggests that LSD administration is associated with sustained improvements in mood and decreased symptoms of anxiety (Muttoni et al., 2019). LSD may be more subjectively challenging than psilocybin, with higher risks of

paranoia, severe anxiety, and panic attacks at high doses, though adverse experiences can be mitigated with proper supports and assessment (Muttoni et al., 2019). Poor clinical trial design is suggested to have exacerbated adverse effects.

3.4 Ketamine

Synthesized in 1962, ketamine has historically been used as a general anesthetic. It has also been implemented into clinical practice for off-label use in unconventional substance use rehabilitation, treatment-resistant depression, and other mental disorders. Ketamine was most commonly used during the Vietnam War when anesthesiologists first became familiar with the substance as an easy-to-administer field medicine that allowed the wounded to protect their airways under anesthetic doses. It was approved in hospitals and for medical procedures in 1970 (Krupitsky & Kolp, 2007). Ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist, affecting synaptic plasticity, neurogenesis, and neural connectivity (Worrell & Gould, 2021). Its water-soluble, aryl-cyclo-alkylamine structure exists in two isomers: the inactive R (-) isomer and the active S (+) isomer (Mion & Villevielle, 2013). The S-ketamine enantiomer is commonly known as esketamine and is used as an on-label medication for depression offered by Spravato® and as a general anesthetic. Oral, subcutaneous (SC), and intranasal (IN) delivery are considered the most practical methods regarding ketamine administration, but it can also be safely administered by sublingual, transmucosal, intravenous (IV), and intramuscular (IM) routes (Andrade, 2017).

While the precise mechanism of action of ketamine is not yet known, it is well established that it is an N-methyl-D-aspartate (NMDA) receptor antagonist (McGirr et al., 2015). Ketamine is reported to affect many neurotransmitter systems, synaptic plasticity, neurogenesis, and neural connectivity (Worrell & Gould, 2021). Additionally, Ketamine is thought to cause an increase in prefrontal extracellular glutamate, leading to dissociation, which may be related to its effectiveness in reducing symptoms of depression (Grabski et al., 2020). When administered in sub-anesthetic doses, ketamine can induce substantial psychoactive effects, sometimes referred to as 'psychotomimetic' to describe typical experiences of dissociation, out-of-body experiences, and changes in experience of time or space (Krupitsky & Kolp, 2007). Ketamine is not a classic psychedelic, but rather a dissociative hallucinogen, yet the subjective effects are often described as 'psychedelic'. Doses may range from one-sixth to one-tenth of what would otherwise be used as general anesthesia to achieve approximately one hour of psychoactive experiences (Krupitsky & Kolp, 2007). Dissociation, feelings of detachment, reduced self-awareness, disorientation, confusion, changes in sensory perception, hallucinations, and memory loss are commonly attributed to psychotherapeutic ketamine dosing (Grabski et al., 2020).

Ketamine elicits anti-addictive benefits to those affected by various treatment-resistant psychiatric conditions (Krupitsky & Kolp, 2007). Administration evokes rapid onset of psychoactive effects with a short duration of action, which can be extended to promote rehabilitation and level of functioning (Krupitsky & Kolp, 2007). An identifying characteristic of therapeutic ketamine administration is the rapid antidepressant effects among those with

treatment-resistant depression (TRD) (Yoon et al., 2019). The antidepressant effects have not been found to be attenuated by naltrexone, a drug used to suppress substance cravings, which has implications for ketamine as an alternative treatment for depressed patients with comorbid substance use disorders (Yoon et al., 2019).

The long-term effects of continual or ascending ketamine dosing remains unknown, suggesting further research. Reported side effects, including dizziness, nausea, memory loss, dissociation, and blurred vision, reduce remarkably or diminish with continual treatment, indicating increasing tolerance with continuous supervised dosing as recommended by a healthcare professional (Yoon et al., 2019). Some patients with treatment-resistant anxiety have been found to remain in remission for beyond three months following final ketamine treatment doses, with few patients reporting re-emergence of partial or full symptoms (Glue et al., 2018). Further studies are required to determine optimal treatment duration for therapeutic use of ketamine (Glue et al., 2018). See Section 4.0 for summaries of the literature on the effectiveness of ketamine-assisted interventions for various mental and substance use disorders and other health-related conditions.

While ketamine is classed as a Schedule I drug in Canada, it is permitted for medical and therapeutic use. The College of Physicians and Surgeons of BC (CPSBC) recently published guidelines that restrict the use of IV ketamine to hospitals or accredited non-hospital medical and surgical facilities (CPSBC 2022). This standard does not apply to other routes of administration in non-accredited facilities, such as intranasal, oral, subcutaneous, and intramuscular. Ketamine is approved by the US Food and Drug Administration (FDA) for sedation and anesthetic uses, and it is commonly used in emergency departments for sedation and pain control (Maguire et al., 2021). In 2019, esketamine, the S-enantiomer of ketamine, was approved by the US FDA to be used intranasally as an adjunct to a newly started antidepressant for treatment resistant depression (Cavenaghi et al., 2021; Maguire et al., 2021). The European Medicines Agency has also approved esketamine use in treatment resistant depression (Grabski et al., 2020). Esketamine is currently under review by Health Canada. There is no current FDA approval of racemic ketamine for the treatment of major bipolar or unipolar depression, but it is used off-label for these conditions (Bahji et al., 2021).

The FDA requires that esketamine be given only in places with a Risk Evaluation and Mitigation Strategy (REMS) in place (McIntyre et al., 2020). It is advised (but not mandated by FDA due to off-label use) that people who are given IV ketamine be monitored for up to 60-120 minutes to ensure safety. (McIntyre et al., 2020). Cost effectiveness analysis for esketamine and IV ketamine will need to factor in REMS implementation and safety monitoring/infrastructure (McIntyre et al., 2020).

3.5 Ayahuasca

Ayahuasca is the Quechua-language name for a psychoactive plant beverage that was developed by peoples in the Amazon region of several South American countries. The psychoactive effects of ayahuasca are generally attributed to two main components: N,N-dimethyltryptamine (DMT) and harmala alkaloids, including harmine, harmaline, and

tetrahydroharmine. Harmine and harmaline are monoamine oxidase inhibitors (MAOI), which attenuate the breakdown of DMT in the gut after oral consumption (as opposed to insufflation or injection). Tetrahydroharmine acts as a serotonin reuptake inhibitor. DMT is found in high concentrations in the *Psychotria viridis* and *Diplopterys cabrerana* plants, while the ayahuasca vine *Banisteriopsis caapi* is a known source of harmala alkaloids. *B. caapi* and *P. viridis* are the two plants that are the most common ingredients for ayahuasca, though it should be noted that recipes change based on regional differences and the name of the tea varies widely according to context (e.g., yagé, natem, caapi, nixi pãe, camarampi, hoasca, daime, among many others). For example, in some preparations, only the ayahuasca vine is used and in other preparations a dozen or more plants may be added. While most ayahuasca preparations include a plant such as *P. viridis* that contains high concentrations of DMT, it is important to note that DMT is but one of dozens of plant-based alkaloids in ayahuasca and thus the pharmacodynamics of the brew is distinct from that of isolated DMT (whether synthesized or naturally extracted). A further difference between isolated DMT and ayahuasca is the ritual setting in which the latter is almost always ingested, which is thought to be integral to beneficial outcomes. While the pharmacodynamics and therapeutic mechanisms of ayahuasca cannot be equated with that of isolated DMT, the literature demonstrates some commonalities in therapeutic outcomes.

For centuries, select Indigenous and mestizo groups in the Amazon rainforest have considered ayahuasca a sacred entity and one of several plant-based healing agents used by ritual specialists (Gow, 1994; Luna, 1986; Tupper, 2011). In the 20th Century, syncretic Christian churches that originated in Brazil, namely Santo Daime, Barquinha, and União do Vegetal (UDV), began using ayahuasca as a religious sacrament (Anderson et al., 2012; Dawson, 2017; Mercante, 2013). The widespread popularity and eventual internationalization of Santo Daime, and to a lesser extent UDV, have been significant factors in the spread of ayahuasca to many other parts of the world, in particular Europe, Australia, and North America, but also to the Middle East, East- and Southeast Asian countries. The globalization of Indigenous and mestizo shamanism and neo-shamanic practices also continue to influence the widespread growth of global ayahuasca-related practices (Labate et al., 2014; Tupper, 2008). Research on the therapeutic value of ayahuasca has focused not only on these varied naturalistic settings (Argento et al., 2019a; O'Shaughnessy, 2017; Thomas et al., 2013) but also in controlled clinical trials in supervised medical settings (e.g., Osório et al., 2015; Palhano-Fontes et al., 2018). This work has included neuroimaging and the use of dried extract to carefully measure composition and dosage (Riba et al., 2006). The overall body of current scientific evidence for ayahuasca's therapeutic potential is pointing towards positive outcomes for substance use and depressive disorders in particular. See Section 4.0 for summaries of the literature on the effectiveness of ayahuasca-assisted interventions for various mental and substance use disorders and other health-related conditions.

Acute psychological effects of ayahuasca, and related in large part to the DMT component, occur approximately 40 minutes following ingestion and peak between 60 and 120 minutes, with subjective effects fading by approximately 4 hours. Users experience alterations in consciousness, and may experience increases in self-confidence, the realization of new perspectives, and reinterpretation of intrapsychic conflicts (Hamill et al., 2019). Visual phenomena stimulated by the combination of DMT and beta-carbolines may be related to

neurochemical changes in both the visual cortex and the claustrum. Uncoupling of claustral and visual cortex sources of edge information may explain the classical DMT visual phenomena. Araújo et al. (2012) found that visions under ayahuasca are based in the activation of networks generally involved with vision, memory, and intention; by enhancing the intensity of recalled images to the same level as open-eye seeing, ayahuasca lends qualities of reality to inner, subjective experiences. Synesthesia is common under ayahuasca, particularly auditory-to-visual effects associated with music and the singing of sacred *icaros* or spiritual hymns of the ayahuasca religions (Labate & Pacheco, 2010; Hamill et al., 2019).

Santos et al. (2007) reported acute effects of ayahuasca one hour after ingestion among a small, double-blind, placebo-controlled sample of long-term (>10 years) participants in the Santo Daime church. State-anxiety (STAI-state), trait-anxiety (STAI-trait), panic-like (ASI-R) and hopelessness (BHS) were all evaluated with standard questionnaires, with statistically significant reductions in hopelessness and panic-like parameters (Santos et al., 2007). The authors speculate that the selective serotonin reuptake inhibition caused by tetrahydroharmine (THH), harmine, and harmaline in *B. caapi* (i.e., the ayahuasca vine itself) may mediate the reduction of these symptoms. The study reported no effects on state- and trait-anxiety, which is likely due to the small sample size of highly experienced users.

Depending on the dose, harmine may be psychoactive on its own and has been implicated as a particularly important compound within ayahuasca, underlying its therapeutic benefit for the treatment of depression and substance use disorders. However, most investigators consider DMT the principal psychedelic substance within the ayahuasca admixture (Brierley & Davidson, 2012). The importance of harmine may be relevant for treatment of substance use disorders specifically as reduced dopamine levels in the mesolimbic pathway interfere with the synaptic plasticity associated with the development and maintenance of these disorders. The postulated mechanisms range from commonly accepted pathways related to agonism of the serotonin 5-HT_{1A/2A/2C} receptors and related modulation of glutaminergic neurotransmission, as well as anti-inflammatory action (see also Galvão-Coelho et al., 2020; da Silva et al., 2021).

Ayahuasca has been shown to upregulate platelet serotonin transporter cells (Callaway et al., 1994; Hamill et al., 2019). Modulation of cortisol levels has also been implicated (Galvão et al., 2018; Santos et al., 2012) as well as modulation of serum brain-derived neurotrophic factor (BDNF), a neurotrophin associated with major depression (de Almeida et al., 2019). The complexity of current hypotheses concerning the therapeutic mechanisms of ayahuasca arises in part due to the typical inclusion of at least two plant species in the ayahuasca brew that together implicate a variety of mechanisms for direct and indirect actions on dopaminergic, serotonergic, and other systems. In addition, the ritual-ceremonial context in which ayahuasca is typically ingested is considered to be relevant to beneficial outcomes (Franquesa et al., 2018; Ona et al., 2021; Perkins et al., 2021), reminding us once again of the importance of set and setting in the association between therapeutic psychedelic use and outcomes. The purgative emetic effects of ayahuasca are also considered to have important cultural as well as pharmacological relevance (see, for example, Fotiou & Gearin, 2019 and Politi et al., 2021).

Current evidence suggests that occasional or repeated long-term use of ayahuasca carries little health risk and no addictive potential (e.g., Hamill et al., 2019; Durante et al., 2021). While the immediate physiological effects may include nausea, diarrhea, increased blood pressure and body temperature, these are temporary for the majority of users. Notably, however, a large-scale survey of ayahuasca drinkers has pointed to longer-term negative effects for a small percentage of users with pre-existing anxiety or depressive disorders (Sarris et al., 2021). Dos Santos et al. (2017) noted a rare incidence of psychotic symptoms consequent to ayahuasca use in their systematic review of case reports, reinforcing the importance of psychiatric pre-screening before use and continuous follow-up.

3.6 DMT + 5-MeO-DMT

N, N-dimethyltryptamine (DMT) is an indole alkaloid naturally occurring in a range of plants and shrubs, and also within animal species (including humans) as an endogenous trace amine transmitter (Carbonaro & Gatch, 2016; Frecska et al., 2013; Hamill et al., 2019). It is a serotonin analogue and substituted tryptamine, both a structural analog and derivative of tryptamine. DMT is a structural and functional analog to other psychedelic tryptamines including 5-MeO-DMT, psilocybin, psilocin, and bufotenine, yet has unique pharmacodynamic properties. As noted above, DMT is a psychoactive compound that is found in many entheogenic practices and rituals in the Amazon basin, particularly known for the widespread ceremonial use of ayahuasca, but also found in the widespread use of psychoactive snuffs such as *yopo* and *willka*, prepared from the seeds of the *Anadenanthera peregrina* or *Anadenanthera colubrina* tree native to Colombia, Venezuela, and Peru (Carbonaro & Gatch, 2016; Coe & McKenna, 2016; McKenna, 2004; Rodd, 2002).

In the early 1990s, Rick Strassman became the first to receive US FDA regulatory approval in almost two decades to administer a psychedelic drug for a human subject clinical trial. His dose-response and phenomenological studies of intravenously administered DMT among healthy volunteers was a key moment marking the initiation of a new wave of clinical studies with psychedelics, often referred to as a renaissance in human psychedelic research (Strassman & Qualls, 1994; Strassman et al., 1994; Strassman, 2001).

As previously mentioned, the administration and pharmacodynamics of DMT are distinct from that of the ayahuasca tea. DMT is often smoked, injected, or insufflated with an almost immediate onset and a relatively short duration of approximately 30 minutes. Ayahuasca, on the other hand, is most often ingested orally as a plant-based decoction and therefore has a delayed onset and longer duration of approximately 4-6 hours. At equivalent doses, the phenomenological intensity of IV DMT is substantially stronger than ayahuasca. Unlike psilocybin, tryptamines such as DMT and 5-MeO-DMT (discussed below) are not orally active due to first-pass metabolism by monoamine oxidase in the gut. Smoked, insufflated, or injected DMT and 5-MeO-DMT are also known to be 10-20 times more potent in humans compared to psilocybin with a much shorter duration of action, lasting less than one hour.

DMT is found in low endogenous concentrations in mammalian (including human) brain tissue (Barker et al., 1981), activating trace amine-associated receptors and can be locally

sequestered in neurotransmitter storage vesicles, assisting in activating serotonin receptors (Carbonaro & Gatch, 2016). Findings suggest that even after kinetic clearance of a dose of DMT, the molecule can still be detected in the bloodstream, suggesting ongoing CNS production of endogenous DMT (Carbonaro & Gatch, 2016). High, local concentrations of DMT can occur in neurons and potentially is widely produced in peripheral organs. Uptake into neuronal cells is conducted by serotonin uptake transporters (SERT) on neuronal membranes (Carbonaro & Gatch, 2016). Since exogenous DMT is not orally active due to rapid degradation by peripheral monoamine oxidase (MAO) enzymes located in the gut, DMT may be smoked or insufflated (i.e., taken as a snuff) to bypass the digestive system. Oral dosing of DMT in ayahuasca results in behavioral and neurochemical effects including reductions in motor activity, intermittent visual effects, cognitive impairment, increased prolactin and cortisol and decreased lymphocytes, increased natural killer cells, and sympathomimetic effects (Bouso et al., 2012; Carbonaro & Gatch, 2016).

As mentioned, smoking DMT allows for the bypass of extensive first pass metabolism by gut MAO enzymes, contributing to strong and rapid effects (Riba et al., 2015). Smoked DMT produces a mean peak effect at 6 min, with a duration of approximately 24 minutes (Barbic et al., 2020). It is hypothesized that smoked DMT, like ayahuasca may introduce the risk of serotonin syndrome when consumed orally with an MAO inhibitor (Fortunato, 2010).

DMT interacts with a variety of serotonin receptors including 5-HT_{2A/2C} and 5-HT_{1A}, as well as with ionotropic and metabotropic glutamate receptors, dopamine, acetylcholine, TAAR, and sigma-1 receptors (Carbonaro & Gatch, 2016; Davis et al., 2020a; McKenna, 2004). Pallavicini et al. (2021) conducted a naturalistic study using wireless electroencephalography in combination with psychometric testing. They found that inhaled DMT significantly decreased the power of alpha (8–12 Hz) oscillations while increasing the power of delta (1–4 Hz) and gamma (30–40 Hz) oscillation frequencies. Gamma power increases are correlated with participant reports of mystical-type experiences (Pallavicini et al., 2021). DMT itself may be a natural participant in biological recuperative and defensive mechanisms, with assumed roles in cell protection, regeneration, and immunity (Frecka et al., 2013). One review suggests possible therapeutic value for DMT in emergency medicine (cardiac arrest), cardiopulmonary resuscitation, intensive care (myocardial infarction), neurology (stroke), neonatal care (in response to poor Apgar score), cardiac surgery, anesthesiology (protecting against transient hypoxia), oncology, and hospice care (Frecka et al., 2013).

DMT does not appear to produce tolerance. One survey of close to 2000 individuals who had used DMT found smoking to be the most common route of administration in naturalistic settings (92%; Winstock et al., 2014). Users rated DMT as having the lowest level of negative effects among all psychedelics and as being stronger in its effects than LSD, psilocybin mushrooms, and ketamine. The rapid onset of DMT via inhalation, combined with its powerful effects and ability to easily titrate doses, does suggest a potential for repeated non-medical use. Nevertheless, DMT users report little urge to use more when already experiencing its effects (Winstock et al., 2014).

In addition to the acute psychological and visual impacts identified above with respect to ayahuasca, DMT has been known to facilitate periods of introspection, altered cognition, and self-insight (Strassman, 2001; Winstock et al., 2014). Encounters with perceived entities occasioned by inhaled DMT (e.g., spirits, guides, aliens, elves and other non-human beings) have also been documented (Michael et al., 2021) and are similar to non-drug induced encounters such as those described in religious and near-death experiences.

Intravenous administration of DMT in one within-subjects placebo-controlled study of 13 healthy individuals was found to evoke the subjective phenomenology associated with near-death experiences (NDEs), including including the subjective feeling of transcending one's body, entering an alternative realm, communicating with 'entities' and themes related to death and dying (Timmermann et al., 2018). IV DMT administration is associated with reduced oscillatory power in the alpha and beta bands and robustly increased spontaneous neural signal diversity (Timmermann et al., 2019). These experiences tend to be considered as among the most meaningful, spiritual, and psychologically insightful lifetime experiences, with persisting improvements in life satisfaction, purpose, and meaning attributed to the experiences (Davis et al., 2020c).

Two case reports documented acute psychosis due to DMT administration in individuals with no previous history of psychosis (Barbic et al., 2020). A recent systematic review recommends psychiatric screening before administration of DMT (dos Santos et al., 2017). Single doses of DMT produced a rapid increase in heart rate and blood pressure (Carbonaro & Gatch, 2016) as well as increased levels of corticotropin, cortisol, prolactin, and growth hormone in humans (Carbonaro & Gatch, 2016). Chronic, intermittent, low doses of DMT have produced antidepressant-like effects as well as enhanced fear extinction learning in pre-clinical rodent studies (Cameron et al., 2019). Given the prevalence of the inhalation of synthetic DMT, including through DMT-containing vaping cartridges, studies on the potential neurotoxicity or long-term effects of ongoing synthetic DMT inhalation use are indicated. Poorly synthesized DMT preparations may contain impurities which when ignited could become neurotoxic, as is the case in the association between leukoencephalopathy (diseased brain white matter) and smoked heroin (Buxton et al., 2011).

See Section 4.0 for summaries of the literature on the effectiveness of DMT-assisted interventions for various mental and substance use disorders and other health-related conditions.

5-MeO-DMT

5-Methoxy-N, N-dimethyltryptamine (5-MeO-DMT) is a related psychoactive tryptamine found in some plants as well as in high concentrations in the venom secreted by *Incilius alvarius* (formerly classified as the genus *Bufo*, commonly known as Colorado Desert Toad) (Davis et al., 2020a; McKenna, 2004). Synthetic, toad, and plant-sourced 5-MeO-DMT are used naturalistically for spiritual and personal purposes among recreational users and may have psychotherapeutic effects (Davis et al., 2018). 5-MeO-DMT is an active compound in yopo and wilka, snuffs derived from the *Anadenanthera peregrina* and *A. colubrina* genuses of perennial

trees, as well as the active compound in snuffs derived from the *Virola* genus of trees (epéna) (Ott, found in DiFonzo & Bordia, 1998). These have been used entheogenically by Indigenous peoples in South America dating to pre-Colombian times (Davis et al., 2018). Plants containing 5-MeO-DMT—such as the leaves of the shrub *Diplopterys cabrerana*—are also added to ayahuasca preparations by some Indigenous peoples of the upper Amazon (McKenna et al., 1984).

5-MeO-DMT is thought to be four to five times more psychopharmacologically active than DMT (Ott, in DiFonzo & Bordia, 1998) and has unique pharmacodynamic and pharmacokinetic properties compared to DMT and other clinically studied psychedelics (Sherwood et al., 2020). 5-MeO-DMT is a potent and fast acting non-selective 5-HT agonist appearing to have a higher affinity for the 5-HT_{1A} receptor subtype and also inhibits the reuptake of serotonin. Onset occurs rapidly within seconds-to-minutes when smoked and peak effects are experienced between 35 and 40 minutes after inhalation or insufflation (Davis et al., 2018).

There is little epidemiological information about the scope of 5-MeO-DMT use, limiting the understanding of the safety, risks, and benefits ascribed to its use. Synthetic sources and vaporization/smoking as the route of administration seem to be most commonplace within the landscape of North American recreational use (Davis et al., 2018). Ott has established that sublingual application is equipotent to intra-nasal ingestion (Ott, in DiFonzo & Bordia, 1998).

Recreational users report low rates of repeated consumption and a variety of moderate-to-strong mystical experiences (Davis et al., 2018). 5-MeO-DMT may have therapeutic value as users report improvements in symptoms related to psychiatric conditions, including anxiety, depression, substance use problems, and PTSD (Davis et al., 2018).

5-MeO-DMT has a relatively good safety profile, a low risk for repeated non-medical use, and low risk for dependence as there is very low demonstrated build-up of tolerance to its effects (Reckweg et al., 2021). One published case report of fatal intoxication following ingestion of 5-MeO-DMT in an ayahuasca decoction (Sklerov et al., 2005) was found to be misleading in a response article from a team of ayahuasca experts (Callaway et al., 2006). A web-based epidemiological survey (n = 515), suggest that 5-MeO-DMT shares a similar risk/safety profile as other tryptamines (Davis et al., 2018). Further, most respondents who experienced challenging subjective effects with either synthetic or toad-derived 5-MeO-DMT did so only to a small degree. Nevertheless, as applies to all currently criminalized substances, there may be an underreporting bias for adverse effects related to the ingestion of 5-MeO-DMT due to concern over legal repercussions. Naturalistic users report moderate-to-strong mystical experiences and reductions in symptoms of psychiatric disorders (Davis et al., 2018). A recent observational study found that a single inhalation of vaporized 5-MeO-DMT preparation resulted in lasting improvements in self-reported life satisfaction, increased mindfulness, and decreased symptoms of psychopathologies (Uthaug et al., 2019). 5-MeO-DMT in combination with iboga has been studied in a retrospective survey, with preliminary results suggesting this modality may offer a novel, rapid-acting, robust and potentially cost-effective treatment for PTSD due to its ability to occasion cognitive flexibility (Davis et al., 2020a).

Reckweg et al. (2021) conducted the first prospective Phase 1 clinical study among healthy volunteers to test the safety, tolerability, and the dose-related psychoactive effects in healthy volunteers (N = 22, 9 female). The study evaluated single, ascending doses of a novel vaporized 5-MeO-DMT formulation at 2, 6, 12, and 18 mg, ingested via inhalation. They also evaluated individualized dose escalation (IDE) at doses ranging from six to 18 mg of 5-MeO-DMT. The overall aim of the study was to determine the dosing regimen of 5-MeO-DMT that would occasion peak experiences, with secondary aims to measure the impact of 5-MeO-DMT on cognitive functioning, mood, and well-being. Outcomes demonstrated that inhalation of a novel vaporized 5-MeO-DMT formulation was safe and well-tolerated in the 2-18mg dose range in both single-dose administration and IDE. No serious adverse events were reported, and all adverse events were mild or moderate and resolved spontaneously. Measures of cognition, mood, and well-being were not affected by 5-MeO-DMT between baseline and seven days after dosing. Cognitive functioning was not significantly different between baseline, two hours after dosing, and seven days after dosing. These results indicate that the psychoactive, psychomotor, and cognitive effects of 5-MeO-DMT are short-lasting and quickly return to baseline after administration (Reckweg et al., 2021). This exploratory Phase 1, two-arm clinical trial reported safety and tolerability among healthy volunteers. The authors report that a Phase I/II study with this same formulation of 5-MeO-DMT in patients with Treatment-Resistant Depression is currently underway (GH001-TRD-102; NCT04698603). This study focus is on safety, tolerability, and anti-depressive effects of 5-MeO-DMT. Further research examining the safety and pharmacokinetics of 5-MeO-DMT administration in humans is recommended.

See Section 4.0 for summaries of the literature on the effectiveness of 5-MeO-DMT-assisted interventions for various mental and substance use disorders and other health-related conditions.

3.7 Mescaline, Peyote and Huachuma

Mescaline is a naturally occurring phenethylamine and 5-HT_{2A/2C} receptor agonist (Johnson et al., 2019). Mescaline can be prepared synthetically or extracted from natural sources, notably from a variety of cacti in North and South America. Mescaline is a lower-potency psychedelic with active doses in the 200–400 mg range and producing subjective effects typically lasting between 8 and 12 hours (Agin-Liebes et al., 2021).

Mescaline (3,4,5-trimethoxyphenethylamine) is a classical serotonergic psychedelic, a naturally occurring protoalkaloid, and substituted phenethylamine. The phenethylamine group is prevalent as a chemical structure in a range of endogenous compounds, including dopamine and norepinephrine (Araújo et al., 2015). Phenethylamines are monamine alkaloids, trace amine, and organic compounds which act as central nervous system stimulants. Mescaline is related to stimulants such as amphetamine and resembles adrenaline (Dyck & Farrell, 2018). One well-known analog of phenethylamine is methylenedioxymethamphetamine (MDMA) (Johnson et al., 2019).

Phenylalkylamine chemicals are themselves subdivided into b1) phenethylamines such as mescaline and b2) constituents of the 2C-X family of phenethylamines, such as 2,5-dimethoxy-

4-bromophenethylamine (2C-B), as well as phenylisopropylamines (“amphetamines”) such as 2,5-dimethoxy-4-iodamphetamine (DOI) (Araújo et al., 2015). N-Benzylphenethylamine (NBOMe) drugs have been sold online since 2010 (Halberstadt, 2017) and are phenethylamines with the chemical addition of an N-benzyl group that increases potency.

Phenylalkylamine psychedelics have been demonstrated to be selective to 5-HT₂ receptors, including 2A, 2B and 2C sites, in contrast to the indolealkylamines (e.g., DMT, 5-MeO-DMT, LSD) which bind non-selectively to serotonin receptors. Agonism of serotonin receptors effects a subsequent adrenergic response. 5-HT receptor affinities of the phenethylamine chemicals are markedly increased by the addition of an N-benzyl group (Halberstadt et al., 2017). Mescaline has a lower affinity for serotonin receptors, thereby requiring larger doses than with tryptamines to produce subjective psychedelic effects and is less efficient in passing the blood-brain barrier, making for a longer onset of action (Jay, 2019).

Phenethylamines and indoleamines have demonstrated cross-tolerance to each other (Araújo et al., 2015). Substituted phenethylamines of the 2C-X family show full agonist affinity at the 5-HT_{2A} and 5-HT_{2C} receptor sites. Effects of these compounds seem biphasic, with stimulation and increased sensory experience at low doses, hallucinations with moderate doses, and high doses resulting in hallucinogenic sensorium (Eshleman et al., 2014).

Mescaline is found in several species of cactus including *Lophophora williamsii* (peyote) endemic to Southwestern United States and Northern and Central Mexico, as well as to a family of cacti of Central and South America colloquially known as Huachuma or San Pedro: *Trichocereus pachanoi* (San Pedro), *T. peruvianus* (Peruvian torch) and *T. bridgesii* (Bolivian torch) (Cassels & Sáez-Briones, 2018). Peyote (péyotl in Náhuatl language) is a small, slow-growing, and hemispherical spineless cactus containing many different alkaloids, though its psychedelic effects have been associated primarily with mescaline (Cassels & Sáez-Briones, 2018).

Dried peyote buttons have been located in archaeological digs and dated to 5800-6000 years before present. Even older, spine clusters of *T. peruvianus* located among cultural artifacts in a cave in northern Peru have been dated to 6200-6800 years ago (Cassels & Sáez-Briones, 2018).

Peyote use among the Indigenous Nahua peoples of Mesoamerica was first described by Spanish friar Bernardino de Sahagún in the late 1600s and associated with large collective ceremonies, individual healing, and with “flower songs” describing a paradisaal garden that is both the source of entheogenic plants and the destination of the journey (Jay, 2019). Indigenous ceremonial use of peyote, as with the sacred teonanactl (i.e., *Psilocybe* genus) mushrooms, was violently persecuted by Spanish colonizers and driven underground. Its use has been notably kept alive by the Huichol/Wixárika peoples of the more remote Sierra Madre Occidental Mountain range. In the 19th century, the ceremonial use of peyote resurfaced as a significant pan-Indigenous religion throughout North America, which would become the legally sanctioned in the context of the Native American Church (Feeney, 2014).

In the Native American Church traditions, which emerged as a syncretic religious practice in the early 20th century, peyote is an ethnomedical therapeutic used as a tonic for multiple ailments, as a stimulant, and most importantly as a spiritual sacrament with associated rituals, including all-night ceremonies overseen by travelling ceremonialists, or “road men” (Blum et al., 1977; Feeney, 2014; Prue, 2013). In addition to ritual ingestion for spiritual purposes, peyote is prepared as a topical medicament for a variety of medical uses, such as pain relief, inflammation, and for wound care.

The first Western medical investigation of a psychedelic compound was Prentiss and Morgan’s 1895 report on peyote, which was supplied to them by James Mooney who had conducted ethnographic studies among the Kiowa along the Rio Grande River valley in the Southern U.S.A (Prentiss & Morgan, 1895). In 1897, mescaline was the first psychedelic alkaloid to be isolated in a laboratory, conducted by chemist Arthur Heffter. By 1919 it was being synthesized and soon gained widespread popularity as both a synthetic and within the context of peyote use (Jay, 2019). Scientific interest in mescaline peaked in the 1930s and subsided with the explosion of LSD research in the 1950s (Rucker et al., 2018). Still, the widespread use of mescaline by scientists, clinicians, artists, and philosophers throughout the 1920s, 30s, and 40s was further amplified by Aldous Huxley’s famous personal essay on his mescaline experience, *The Doors of Perception*, published in 1954 (Dyck & Farrell, 2018). Canadian research combining mescaline and LSD was conducted in Weyburn Saskatchewan, in many ways shaping the future modality of psychedelic-assisted psychotherapy (Dyck & Farrell, 2018).

Mescaline has a half-life of approximately six hours and is almost completely eliminated from the human body within 48 hours. Urinary excretion peaks at two hours. (Cassels & Sáez-Briones, 2018). *In vivo* effects in animal models include hypolocomotion, increased startle reaction, temporal disruption, and increase in headshaking (a distinctive indication of 5-HT_{2A} activation) but no effect on rearing or grooming behaviours (Cassels & Sáez-Briones, 2018). Animal studies further suggest mescaline alters sociality and endocrine regulation (Kyzar et al., 2017).

Subjective effects of mescaline include vivid imagery, intensification of colour, geometrical patterns and spatial distortions, dizziness, nausea, increase in body temperature, physical prostration, as well as cardiac and respiratory stimulation (Cassels & Sáez-Briones, 2018). Surveys of naturalistic use find self-reported improvements in mental health including reductions in anxiety, substance use, depressive and PTSD symptomology, as well as enduring positive life changes (Agin-Liebes et al., 2021). At a population health level, the use of mescaline may be a protective factor associated with better mental health status (Johansen & Krebs, 2015; Uthaug et al., 2021a).

Molecular imaging studies using PET and SPECT demonstrated various signs of increased brain activity during acute effects of mescaline, as well as psilocybin (Johnson et al., 2019). Nevertheless, brain imaging via fMRI, EEG, and MEG measures consistently demonstrates classic psychedelics to initiate an overall reduction in activity in the brain, though Johnson et al. (2019) review the acute effects on systems-level neural functioning and relative increases in activity in frontal brain regions. Like ayahuasca and psilocybin, oral administration of mescaline induces excitatory effects in frontolateral/frontomedial cortex, medial temporal lobe, and the

amygdala, all areas involved in personal self-awareness (dos Santos et al., 2016a). One open-label study on mescaline showed significant increases in cerebral blood flow in frontal cortical regions at time of peak drug effect, with decreased posterior cortical regional activity (dos Santos et al., 2016a; see also Johnson et al., 2019 for an updated discussion).

Mescaline has been the chemical basis for the development of an impressive number of synthetic psychedelics (Shulgin & Shulgin, 1991), but pharmacological research remains fragmentary. In contrast to psilocybin and LSD, there are no recent clinical trials investigating the potential clinical benefit of mescaline, despite that cultural and religious use suggest psychological benefits and therapeutic potential. Further, issues of sustainability and the need to protect sanctioned Indigenous religious access to peyote shape current popular discourse around mescaline (see discussion below in section 7.1).

Mescaline has been associated with improvement in alcohol use disorder and depression (Agin-Liebes et al., 2021). See Section 4.0 for summaries of the literature on the effectiveness of mescaline-assisted interventions for various mental and substance use disorders and other health-related conditions.

3.8 MDMA

Identified by the ingredient which comprises the recreational synthetic drug known as ecstasy, 3,4-methylenedioxymethamphetamine (MDMA) has prompted an increase in clinical research over the last 15 years. MDMA produces a non-selective activation of monoamine receptors, acting as a potent MAO releaser (Roseman et al., 2014). It is not considered within the group of classic psychedelics/hallucinogens, since its mechanisms are primarily associated with general serotonin release rather than direct 5-HT_{2A} receptor agonism (Nichols, 2016). Its subjective effects also differ substantially from classic psychedelics, hence its designation as an ‘entactogen’ rather than psychedelic/entheogen. Nevertheless, there is partial overlap with classic psychedelics in its mechanisms and effects, to the extent that it is often referred to colloquially and in drug surveys as a psychedelic (Johnson et al., 2019). In addition to its MAO agonism and serotonergic effects, MDMA impacts other neurotransmitter systems and brain chemistry implicated in animal models and human studies as being associated with drug-taking, mood, and anxiety (e.g., norepinephrine, dopamine, buprenorphine) (see Jerome et al., 2013, for a review of this literature).

MDMA has demonstrated efficacy in the treatment of various mental disorders. In the late 1970s and early 1980s before MDMA was classified as a Schedule 1 compound, it was used in conjunction with psychotherapy by an estimated 4000 psychiatrists and psychologists (Mithoefer et al., 2016; Stolaroff, 2022). MDMA was then recognized as an ‘entactogen’, alluding to its tendency to enhance self-awareness, social cognition, and a general feeling of connectedness with oneself (Mithoefer et al., 2016). Subsequent investigators have suggested that MDMA is an ‘empathogen,’ which describe its demonstrated effects on empathy and prosocial feelings in controlled studies (Bedi et al., 2010). In the mid-1980s, MDMA was classified as a Schedule I substance, leading to regulatory prohibitions and restricted funding that limited research on MDMA and psychotherapy for approximately 20 years (Mithoefer et al., 2016). Decades of

advocacy and largely philanthropic funding has allowed for a rise in pre-clinical research, retrospective studies, and Phase 1, 2, and 3 trials.

Phase I trials with healthy volunteers were initially conducted to assess the risks associated with MDMA consumption in both recreational and non-recreational users. Substantial investment by the US National Institutes of Health from the mid-1980s to early 2000s elicited an investigation pertaining to MDMA-induced serotonin and dopamine neurotoxicity (Mithoefer et al., 2016). Many flaws in the methods used elicited further research with more rigorous research designs to more appropriately assess the risks and benefits of its use (Johansen & Krebs, 2012).

Encouraging results from MDMA administration have been shown in the treatment of refractory PTSD, social anxiety in autistic adults, and end-of-life distress. The psychoactive effects of MDMA have been found to considerably elevate mood, increase sociability and interpersonal communication, and facilitate imagination and memory, associated with raised levels of monoamine neurotransmitters in the brain (Sessa et al., 2021). MDMA acts to increase oxytocin levels, ventromedial prefrontal activity, and norepinephrine and cortisol circulation, which are posited to strengthen the therapeutic alliance, emotional regulation, and extinction of learned fear associations (Johansen & Krebs, 2009). Neuroimaging studies have demonstrated an association between improved negative memory processing and reduced amygdala and hippocampus activity, indicating that the elevated self-awareness and cognitive benefits of MDMA could be beneficial as an adjunctive treatment for alcohol addiction and comorbid psychiatric disorders (Sessa et al., 2021). Long-term follow-up data from the first completed trial of MDMA-assisted psychotherapy for chronic, treatment-resistant PTSD demonstrated significant symptom relief with no reported harm or side-effects of participation (Jerome et al., 2020). Significantly, the prominent subjective and physiological effects of MDMA, as with most other psychedelic compounds, make blinding to investigators and participants more difficult than in studies pertaining to other classes of drugs. Attempts to address this problem with the use of low doses of MDMA as an active placebo proved unsuccessful, since low doses led to an increase in adverse effects such as anxiousness (Mithoefer et al., 2016). This has instigated questions about how to design an appropriate placebo-controlled trial for highly psychoactive substances. See Section 6.2.1 for further discussion on clinical trial design and placebo responses.

MDMA received FDA “breakthrough therapy” status for treatment of PTSD in 2017 and is currently in Phase 3 clinical trials for PTSD at multiple sites in the U.S., Canada, and Israel. A Phase 1 trial in the United Kingdom is also underway, investigating MDMA for the treatment of alcohol use disorder. See Section 4.0 for summaries of the literature on the effectiveness of MDMA-assisted interventions for various mental and substance use disorders and other health-related conditions.

3.9 Iboga and ibogaine

Iboga (*Tabernanthe iboga*) is an evergreen bush native to equatorial West Africa, specifically the tropical jungles of Cameroon, Gabon, Angola, and the Republic of Congo. It has been used extensively in ritual context within the Fang Bwiti, Mitsogo, and Mbiri spiritual disciplines. Its use

among Bwiti practitioners in Gabon is perhaps the most well-studied and popularly known. The strong psychedelic effects of iboga are attributed to the indole alkaloid *ibogaine*, which was first isolated in 1901 and was used medically as a neuromuscular stimulant and antidepressant in France from 1939 to 1970 under the trade name Lambarène. In 1962, a young heroin-addicted man in New York City named Howard Lotsof discovered that ibogaine was highly effective in relieving his heroin dependence as well as avoiding withdrawal symptoms that normally occur after sudden cessation of use. Lotsof and his network spent decades attempting to promote research on ibogaine for opioid dependence. Pilot research in animal models in the late 1980s indicated the efficacy of ibogaine in opiate withdrawal, and in 1993 the US National Institute on Drug Abuse (NIDA) developed its own Phase I/II clinical protocol for the use of ibogaine with cocaine dependence (Alper et al., 2001). After years of attempting research in the US, Dr. Deborah Mash, Professor of Neurology at the University of Miami School of Medicine, initiated an ibogaine treatment program in St. Kitts, mainly targeted toward addiction to heroin and cocaine (Alper et al., 2001), which has since treated hundreds of patients. Treatment centers that use ibogaine for detoxification and addiction rehabilitation for a variety of substances currently operate in Mexico (Brown & Alper, 2018), the Netherlands, South Africa, New Zealand (Noller et al., 2018), Portugal, and Canada.⁷ Research results with respect to treatment of opioid use disorders have shown considerable promise but further study has been hampered by very challenging safety and risk factors within the treatment protocols. See Section 4.0 for summaries of the literature on the effectiveness of iboga and ibogaine-assisted interventions for various mental and substance use disorders.

Ibogaine (12-methoxyibogamine) metabolizes into the active metabolite of noribogaine (2-hydroxyibogamine), and both are known for anti-addictive and anti-craving effects. Ibogaine binds to NMDA receptors, κ -opioid, μ -opioid and σ_2 , serotonin (5-HT₂ and 5-HT₃), muscarinic (M1 and M2) receptors and monoamine uptake sites, and nicotinic acetylcholine receptors (Mačiulaitis et al., 2008, p.186). Noribogaine acts on the NMDA receptors (though not as potently as ibogaine), is a serotonin reuptake inhibitor, a κ -opioid receptor agonist, and blocks neuronal nicotinic receptors (Maillet et al., 2015). While ibogaine may cause tremors and bradycardia in human patients, noribogaine is considered to be well tolerated by humans and a better candidate for clinical drug development (Koenig & Hilber, 2015; Maillet et al., 2015). Noribogaine has also been observed to moderate the analgesic action of morphine while also preventing tolerance to its effects (Maillet et al., 2015).

3.10 Cross-cutting themes regarding mechanisms of action

Following this brief overview of the main substances under discussion in this report, the following section will address overarching themes concerning mechanisms of action. Here we address common explanations for neuropharmacological and psychological mechanisms of

⁷ Portugal: <https://ibogainetreatment.eu/>, Canada: <https://clearskyibogaine.com/ibogaine-canada/>

action, as well as the role of transcendent experiences, set and setting, and their role in the meaning response.

Neuropharmacological

In concert with the clinically focused work, several advances have been made in understanding the basic mechanisms underlying purported therapeutic benefits of psychedelics. While it is well beyond the scope of this report to go deeper into basic neuropharmacological mechanisms, suffice to say that the work to date highlights several plausible mechanisms and provides a solid foundation for continued advances in this area. Further, psychedelics present an opportunity to investigate the neural correlates and hemodynamics of various psychological states through the use of brain imaging techniques such as electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG), arterial blood labelling (ABL), and positive emission tomography (PET) (Carhart-Harris et al., 2012).

Considerable research has focused on specific neurotransmitter systems, in particular work on tryptamine-based substances otherwise known as the broad class of ‘classic’ or serotonergic hallucinogens (Araújo et al., 2015). These substances exert their effects primarily through agonism of 5HT_{2A} serotonin receptors which in turn impact dopaminergic signaling, both of which are clearly implicated in the reward system and changes in brain pathways associated with substance use and addictive behavior (Volkow & Morales, 2015). Johnson et al. (2019) summarize the many other neurotransmitter systems implicated in this broad class of psychedelic substances.

Based on neuroimaging and microphenomenological analysis, a well-supported theory to explain psychotherapeutic effects of psychedelics cites the important role of resting state networks (RSNs), specifically the default mode network (DMN). The so-called entropic brain hypothesis explains that under the influence of psychedelics, the entropic state of brain activity is heightened, enabling the brain to be more sensitive to set and setting and perceptions of connectedness (Carhart-Harris et al., 2014; Carhart-Harris et al., 2018b; Carhart-Harris, 2018; Palhano-Fontes et al., 2015; Pasquini et al., 2020). fMRI, EEG, and MEG data supporting this hypothesis suggest that decreases in modularity and integration of brain networks is associated with increased entropy in the brain, i.e., increased randomness or uncertainty (Carhart-Harris et al., 2014). However, Johnson et al. (2019) argue that further studies which account for the formation of new local networks and increases in distinct patterns in the brain must be considered in addition to increased entropy.

Psychedelic drugs commonly stimulate 5-HT_{2A} cortical layer V pyramidal neurons, triggering unique cellular signaling pathways, altering epigenetic expression, and modulating the activity of dopaminergic, GABAergic (the inhibitory gamma-aminobutyric acid) and other key neurochemical systems. A cortical desynchronization across various key brain regions results, creating a time-bound entropic experiential state of heightened neuroplasticity which disrupts previously established and potentially pathological brain network patterns. Classic psychedelics further stimulate the dopaminergic system principally via D2 receptors and indirectly stimulate the glutaminergic and GABAergic systems (Calvey & Howells, 2018). As mentioned,

serotonergic psychedelics occasion the *desynchronization* of typical brain states, resulting in a state of entropy (uncertainty), and what Carhart-Harris (2018) has referred to as the relaxation of previously conditioned expectations and beliefs. Such a state of “criticality” is associated with neural plasticity and improved psychological outcomes (Carhart-Harris et al., 2016b; Muthukumaraswamy et al., 2013).

Several neuroimaging studies also suggest that the altered states of consciousness produced by many of the substances of interest create a disruption or interruption of the repetitive, rigid, and pathological pattern of negative and compulsive thoughts present in mood, anxiety, and substance use disorders, contributing to changes in perspective, values, and behavior (see summary of this literature by dos Santos et al., 2016b). These findings complement earlier contributions by Vollenweider and Kometer (2010) on neurobiological mechanisms underlying psychoactive substances in the same family of psychedelics (e.g., LSD, ketamine) that impact glutamate neuroplasticity and other mechanisms implicated in the treatment of mood disorders. Clinical research has indicated that the effects of psychedelics on the DMN is a potential mechanism for such improvements in mood, perspective, and behavior.

Mechanisms associated with neuroplasticity and neurogenesis have been implicated by several studies of this family of psychedelic compounds (e.g., Morales-García et al., 2017; 2020). Important activity in brain regions involved in emotional processing and introspection is also implicated (Kometer et al., 2012; Kraehenmann et al., 2015), including the functions of the interoceptive system that modulates approach or avoidance of environmental stimuli. The interoceptive system, closely embedded in the insula region of the brain, seems to be particularly important in drug use disorders as it processes information about body state and external stimulation, makes a prediction about risk and benefit, and then launches a behavioral response to achieve the desired goal (Paulus et al., 2013). Clearly, the hypothesized neuropharmacological mechanisms vary somewhat by the psychedelic substance under consideration as well as the targeted outcome of interest, for example, mood, anxiety, or substance use.

Psychological and Transcendental Mechanisms

Well-formulated psychosocial and spirituality-based hypotheses compliment the understanding of the underlying neuropharmacological mechanisms. To date, the work of Liester and Prickett (2012), Prickett and Liester (2014), and Bogenschutz and Pommy (2012) provide the best syntheses from the biomedical perspective of putative mechanisms underlying psychedelics that go beyond neuroscience to include psychological as well as the so-called mysticomimetic, transcendental, or “peak” experience.

There are several hypothesized mechanisms triggered by the aforementioned neurochemical processes which, in turn, are thought to increase positive mental health and other outcomes. This line of thinking is well-represented by the work of Castelhana et al. (2021) who reviewed functional and molecular imaging studies of the effects of the classic tryptamine psychedelics (e.g., LSD, psilocybin, DMT, ayahuasca) in various regions of the brain. They found strong neuromodulating effects in key regions involved in mental imagery and affective regulation.

Similarly, the work recently reported by Doss et al. (2021) assessed the relationship between cognitive and neural flexibility, aiming to better understand the enduring effects of psilocybin-assisted therapy. Davis et al. (2020b) found in a cross-sectional survey that increases in psychological flexibility fully mediated the effect of mystical and insightful experiences on depression and anxiety following the use of psychedelics. Watts and Luoma (2020) suggest that the psychological flexibility model (PFM) is useful for guiding preparation and integration in psychedelic-assisted therapy. They propose the ACE model (Accept, Connect, Embody), which rearranges the six psychological flexibility processes in an acceptance triad and a connection triad. The ACE model is currently in use in a trial of psilocybin for major depression. Also in clinical trials with psilocybin, Sloshower et al. (2020) are proponents of Acceptance and Commitment Therapy for its mindfulness-based focus on acceptance in addition to a behavioral approach to psychological flexibility (see also Guss et al., 2020). Koslowksi et al. (2022) summarize the usefulness of cognitive behavioral therapies such as these for psychedelic-assisted psychotherapy, noting that psychodynamic, humanistic, and hypnotherapeutic methods are also worthy of attention.

Hypotheses underlying psychological mechanisms reflect, for example, changes in perception, sense-of-self, ideation, and release of repressed memory, often in the form of intense visualization, all of which are consistently reported across studies with psychedelics. Also emphasizing psychological aspects, Domínguez–Clavé et al. (2016) reviewed research on psychological variables related to outcomes after drinking ayahuasca and concluded that enhanced mindfulness related to acceptance and the ability to take a detached view of one's own thoughts and emotions, including safe exposure to emotional events, were important factors in successful treatment of impulse-related, personality, and substance use disorders, and also in the handling of trauma. Similarly, Dakwar et al. (2019) reported that a single infusion of ketamine combined with mindfulness-based behavioral modification improved treatment outcomes among cocaine-dependent adults. Approaches such as these recognize that psychedelics are hypothesized to naturally stimulate mindfulness and aim to actively enhance its depth and sustainability as a practice. Franquesa et al. (2018) emphasize underpinning psychological variables related to “de-centering” values and self, while Timmermann et al. (2018) have focused on the phenomenological relationship between DMT-induced experiences of ego dissolution (often characterized by ‘ego death’) and near-death experiences (NDEs), the latter of which are known to confer long-term positive changes in well-being. Feeney (2014) postulates the therapeutic efficacy of psychedelics is created by the heightened affective experience, new cognitive mastery, and the acts of self-insight and self-disclosure.

Preparation, provision of safety and support and psychological integration of the psychedelic experience are implicated as important contributors to positive outcomes (Perkins et al., 2021). Psychotherapeutic processes such as group sharing, art therapy, and/or professional psychosocial support and interpretation are noted to be particularly important for positive outcomes in psychedelic-assisted treatment and rehabilitation for substance use disorders (Loizaga-Velder & Pazzi, 2014; Loizaga-Velder & Verres, 2014). Ethnographic work reported by Talin and Sanabria (2017) concerning substance use-related recovery experiences with ayahuasca highlight the importance of collective ritual-ceremonial healing spaces and practices for therapeutic outcomes, which again points to the importance of the therapeutic content and

context. The concept of integration may differ depending on sociocultural, ceremonial, and therapeutic context, or even the substance being used (Callon et al., 2021; Diament et al., 2021).

The importance of the transcendental, or “peak”, mystical experience has been emphasized as a mediating factor in treatment outcomes for many study participants and healthy members of the general public (Johnson et al., 2019; James et al., 2020). In early research, high dosing of LSD in the therapeutic context was intentionally aimed at achieving the so-called “psychedelic peak experience” (Grof et al., 2008). More recently, the therapeutic value of mystical experiences has been reported in the use of psychedelics for alleviating depression and anxiety in terminally ill cancer patients (Griffiths et al., 2016) and other therapeutic processes (Majić et al., 2015). Similarly, the intensity of mystical-type experiences during psilocybin-assisted therapy has been correlated with treatment outcomes for alcohol dependence (Bogenschutz et al., 2015) and nicotine dependence (Garcia-Romeu et al., 2014; Johnson et al., 2014; 2017a). As noted earlier, in the effort to explain such results Carhart-Harris et al. (2018b) emphasize the different dimensions of “connectedness” that arises in the psychedelic experience (e.g., connected to nature, to others, or the larger universe in a mystical way). Kjellgren et al. (2009) characterize the stages of the ayahuasca experience as often culminating in a deep transpersonal experience and fundamental changes in worldview, personal development, interests, and orientation to life in general. Importantly, the place of entheogens in the cosmovision of various Indigenous cultures is such that these substances serve as an important medium for interaction with both human and non-human entities in the animal, plant, and spirit realms which are considered key to a healing process via the healer and/or community. For example, in pre-colonial and some current Indigenous contexts of Amazonian ayahuasca use, the substance itself was typically consumed only by the healer, thus the “mechanism” of healing was independent of the pharmacological properties of the substance or derivative psychological impact on the patient (Brabec de Mori, 2011; 2021). In subsequent sections we return to the differences between Western and Indigenous worldviews and implications for further understanding the mechanisms and the healing potential of these entheogenic substances.

Recently the “peak experience” mystical hypothesis has been linked to the model of “quantum change” which is described as a sudden and compelling insight into life problems and circumstances leading to substantial and sustained changes in behaviour and perception. Johnson et al. (2019) draw comparisons to a range of psychological theories but also note the fundamental distinction between quantum change and current tenets of behavioral science, the latter typically ascribing therapeutic benefit to small incremental steps. The early writings of Bill Miller concerning the ability of meaningful spiritual experiences to trigger spontaneous, dramatic, and lasting “quantum change” in addictive behaviors (Miller, 2004; Miller & C’de baca, 2001) also stands in comparison to these prevailing views and is consistent with the experience described by some participants in psychedelic clinical research and healthy members of the general population.

Set, Setting and Emerging Hypotheses on Integrated Mechanisms

While it is important to understand the underlying neuropharmacology and associated mechanisms more fully, they are only part of a complex interplay between putative mechanisms related to the dose and quality of the substance ingested and non-pharmacological factors such as the individual characteristic of the person (set) and the social-environmental context of the experience itself (setting) (e.g., Loizaga-Velder & Pazzi, 2014; Loizaga-Velder & Verres, 2014; Uthaug et al., 2021b). The set and setting hypothesis holds that the “set” of the user (their expectations, personality structure, the availability of interpersonal support, mental and emotional state) and the “setting” of the use (both the immediate physical setting but also the social environment and cultural values assigned to the drug, as well as context of use, whether therapeutic, spiritual/ceremonial, recreational, etc.) combine with the basic potential pharmacology of the “substance” (i.e., the psychoactive substance) to create the drug experience (Studerus et al., 2011).

Timothy Leary first identified the importance of set and setting during his psilocybin research at Harvard in the early 1960's. As Ido Hartogsohn points out, “no other group of drugs appears to be as plastic and responsive to conditions of set and setting as the psychedelics—mind-manifesting drugs whose very name points to their character as nonspecific reflectors of extra-drug conditions” (Hartogsohn, 2017).

How have researchers responded to the obvious importance of these internal and external contextual factors? An integrative approach has been to study the connection between individual and environmental factors (i.e., set and setting) at the level of the neuropharmacology of the brain itself. Citing the original ideas postulated by Carhart-Harris and Nutt (2017), Carhart-Harris et al. (2018b) focused on increased 5-HT_{2A} receptor signalling as mediating cortical plasticity and an associated sensitivity to internal (i.e., endogenous processes and pre-existing mental context) and external influence (i.e., the environment). That is to say, the investigators have hypothesized neuropharmacological mechanisms to potentially explain why set and setting are so influential in psychedelic experiences.

With the belief that the fundamental mechanisms of action are dependent on the substance itself, specifically certain potent alkaloids that interact with different neurotransmitter systems, many clinical researchers focus their attention on teasing out the “non-drug” or extrapharmacological factors associated with measured outcomes. Through this line of thinking, set and setting are often considered to be “noise” to be minimized, if not removed completely as a kind of confounder. This is essentially the aim of an RCT: to provide evidence for the safety and efficacy of a specific isolated molecule or intervention while also reducing or explaining away so-called confounding factors or bias such as individual expectations, therapeutic or ceremonial context, and so forth. In the case of placebo controlled RCTs, the influence of set and setting present significant challenges in blinding both participants and researchers, understanding the influence of expectancies, as well as delineating effects of the substance itself from the psychotherapeutic interventions (Johnson et al., 2008; Muthukumaraswamy et al., 2021; Rucker et al., 2018; Sellers et al., 2018). Some research programs use low-doses or microdoses of the substance under investigation as the active

placebo in double-blind, placebo-controlled RCTs as a means to more assuredly isolate the causal pharmacological agent from internal and environmental factors, including adjunct psychotherapeutic interventions (Galvão-Coelho et al., 2021). See Section 6.2 for further discussion on trial design.

A more real-world approach recognizes the importance of the interplay of various pharmacological, psychological and spirituality-based mechanisms and aims to actively assess their mutual importance through study design, statistical adjustments and/or qualitative methods (Beaussant et al., 2021). This is similar to the search for so-called “critical ingredients” in other areas of mental health research (Bond & Drake, 2015; Holter et al., 2004). Feeney (2014) has recently presented a robust Total Drug Effect model whereby the power of psychedelic experiences is conditioned by five variables: drug, set, setting, but also belief in the healer/healing modality as well as the cultural matrix informing beliefs, attitudes, and values about psychedelics. This approach also speaks to the value of framing psychedelic-assisted therapy as a “complex” intervention, the study of which could draw upon research models such as realistic evaluation and complexity theory (Rog, 2012).

Still another approach, aligned with an Indigenous worldview, resists outright the tendency to de-construct the psychedelic-assisted intervention and considers the wholistic interaction of set, setting and substance combination to be part of the “technology” that facilitates a connection to spiritual entities or a spirit world. This experience of connection is the so-called active ingredient or “mechanism” for healing, not any one part of the process to get there.

Regardless of your viewpoint on these various approaches to understanding the pathways to therapeutic benefit, it is important to recognize the value of these differences in the search for integrative explanatory models.

4.0 Results: Effectiveness of Treatment and Support

4.1 Outcomes Related to Substance Use Disorders

Substance use disorders, and related comorbidity exact an exorbitant impact on the burden of healthcare and associated costs to society. In Canada, in 2014, substance use cost Canadians more than \$14 billion, with alcohol and tobacco use accounting for about 70% of those costs (Canadian Centre on Substance Use and Addiction, 2018). The US National Institutes of Health documented that in 2013, 16.5 million Americans reported heavy drinking, 55.8 million were current cigarette smokers, and 24.6% were current illicit drug users. The costs of non-medical use of these substances have been estimated at \$740 billion USD annually, reflecting impacts on crime, work productivity, and health care (National Institute on Drug Abuse, 2017). Data which reflect similarly high costs are reported for the UK and Europe, especially with respect to alcohol (Home Office, 2012) and tobacco (World Health Organization, 2007). Globally, alcohol use is widely regarded as a leading risk factor for death and disability (Griswold et al., 2018; Shield et al., 2020), and accounts for a significant loss in global GNP (Skolnik, 2015). National, sub-national, and municipal jurisdictions struggle to manage these burdens of health and related costs, while also providing the direct services and supports to those seeking assistance for substance use disorders and the many related comorbidities.

Rates of illicit drug poisoning morbidity and mortality have continued to rise across North America (Donroe et al., 2018; Vashishtha et al., 2017). In Canada specifically, 19,355 individuals died from toxic street drugs, especially illicit opioid-related causes between January 2016 and September 2020, and the rate of opioid-related mortality increased 106% between 2016 and 2020 (January-September; Special Advisory Committee on the Epidemic of Opioid Overdoses, 2020). The growth of morbidity and mortality from even greater adulteration and toxicity of street drugs has also been accelerated by the COVID-19 pandemic (Canadian Institute for Health Information, 2021).

There have been several narrative, scoping and systematic reviews examining the therapeutic value of psychedelic substances in ameliorating substance use disorders. Some comprehensive reviews include substance use disorders in the context of mental disorders more generally (e.g., Belouin & Henningfield, 2018; Reiff et al., 2020; Rucker, 2015; Tupper et al., 2015), while others noted below are quite targeted. The most comprehensive reviews cover epidemiological studies, mechanisms, safety considerations, treatment efficacy and regulatory challenges (see Johnson et al., 2019 for an excellent example). Reviews are also typically inclusive of clinical trials (e.g., Dakwar et al., 2020) as well as observational studies (e.g., Thomas et al., 2013), and health outcome-oriented studies and epidemiological investigations focused on users of psychedelic substances in the general population (e.g., Garcia-Romeu et al., 2019). Some reviews have focused on substance use disorders as a general class (e.g., DiVito & Leger, 2020; Nigam & Pandurangi, 2021), others focus on specific substance use disorders, most commonly alcohol or opioid use disorders (see Fluyau et al., 2020 and Worrell & Gould, 2021,

respectively). Some reviews focus on effectiveness of one particular psychedelic substance such as ibogaine (e.g., Brown, 2013); ketamine (e.g., Jones et al., 2018); MDMA (Jerome et al., 2013); psilocybin (de Veen et al., 2017); 5-MeO-DMT (Davis et al., 2018); or ayahuasca (e.g., Nunes et al., 2016; Barabasz-Gembczyk & Kucia, 2020), while others speak to the effectiveness of “classic” hallucinogens in general (Bogenshutz & Johnson, 2016; Johnson et al., 2019) or other groupings of interest (e.g., Winkelman, 2014).

Below we summarize key findings across the extant reviews published between 1990 and 2021 as well as recent work that may not have been captured by these reviews. The general consensus among these scholars is that there is sufficient evidence to warrant further investigation, especially given the high percentage of people who do not respond well to current treatment alternatives (i.e., are treatment refractory), and in the face of the global disease burden of substance use disorders and other psychiatric conditions. In short, the arguments to rejuvenate this research domain have been cogent and cautiously optimistic with respect to substance use disorders.

We commence with a discussion of the research evidence with respect to tobacco use disorder followed by brief sections specific to alcohol use disorder, opioid use disorder, stimulant use disorder and cannabis use disorder, the latter two having importance but a much thinner research base at present. The flow of information is organized by the mental health condition in question and the psychedelic substances that are considered to have potential for its treatment and recovery. Both naturalistic and clinical studies are considered in each section, rather than separated by methodological differences.

4.1.1 Tobacco Use Disorder

Psilocybin

Johnson and colleagues at John Hopkins University studied the effects of psilocybin for the treatment of tobacco dependence (Johnson et al., 2014). As an initial pilot study, they employed an open-label design and involved 15 participants who smoked at least 10 cigarettes per day and had multiple previous unsuccessful quit attempts. After receiving only two or three sessions of psilocybin-assisted psychotherapy, 12 of the 15 participants were totally abstinent at six months follow-up, verified both by self-report and biologically through measures of exhaled carbon monoxide and urinary cotinine levels. The transcendent or mystical-type experience during the sessions, measured with a validated scale, was positively correlated with smoking cessation outcomes (Garcia-Romeu et al., 2014).

Noorani et al. (2018) recruited 12 participants from the original pilot study described above and conducted follow-up interviews on average 30 months after initial study completion in order to further investigate potential mechanisms of change through qualitative assessment of their personal experiences and longer-term outcomes. Importantly, participants identified that benefits gained overshadowed any short-term withdrawal symptoms. Beneficial effects that persisted well beyond the acute drug effects included insights into self-identity and reasons for smoking, feelings of inter-connectedness, awe, and curiosity. Preparatory counselling was

identified as an important contributing factor to maintaining abstinence. In addition to tobacco use cessation, other benefits reported included aesthetic appreciation, altruism, and pro-social behaviour.

4.1.2 Alcohol Use Disorder

LSD

At the close of the earlier period of psychedelic research in the 50's and 60's, the state of knowledge was perhaps best summarized by the closing sentence of the review of LSD research by Mangini (1998): "What is now known about LSD therapy for alcoholism neither provides evidence of its efficacy, nor assurance that its maximum therapeutic potential has been achieved" (p. 414). A measure of renewed confidence in that earlier work has come from more recent reviews of that work (Dyck, 2008) and, in particular, a systematic review of six well-done controlled trials of the efficacy of LSD for the treatment of alcoholism (Krebs & Johansen, 2012). This latter review considered findings from studies done in the 1960s and early 1970s, which compared treatment with LSD to controls ($n = 536$), with results favoring the LSD treatment in objectively measured improvements in chronic or otherwise problematic alcohol use.

Psilocybin

Bogenschutz and a New Mexico-based team (Bogenschutz et al., 2015) combined pre-post motivational enhancement therapy with one or two open label sessions of psilocybin to treat a small sample ($n = 10$) of people with active alcohol dependence. Among those completing the study, self-reported drinking days and heavy drinking days were reduced by more than half of the baseline measures. Qualitative content analysis of case notes made during debriefing sessions highlighted the multiplicity of factors potentially associated with treatment outcome, including transcendent experiences, ego-dissolution, enhanced motivation, commitment to change, and changes in the perceived relationship to alcohol (Nielson et al., 2018).

MDMA

Jerome et al. (2013) provided an overview of the potential role of MDMA in the treatment of substance use disorders, drawing links to the pharmacological and subjective effects of MDMA and the promising data of related co-morbidities, in particular PTSD. Years later, Sessa and colleagues (2021) reported on the first open-label study of MDMA for alcohol use disorders with a particular focus on safety and tolerability of MDMA-assisted psychotherapy for clients post-detoxification. Outcomes related to drinking behaviour, quality of life and psychosocial functioning were evaluated with 14 patients who completed community-based alcohol detoxification followed by an eight-week course of recovery-based outpatient therapy. Participants received two sessions with MDMA with psychological support provided before, during, and after each session. Outcomes were assessed for nine months after alcohol detoxification. Results showed the MDMA treatment to be well-tolerated by all participants with no unexpected or enduring adverse events. Psychosocial functioning improved across the cohort and, at nine months post-detox, the average units of alcohol consumption by participants

was 18.7 units per week compared to 130.6 units per week before the detox. The study provides preliminary support for the safety and tolerability of an MDMA-based intervention for alcohol-use disorder post-detox.

Ayahuasca

There have been no clinical trials studying the efficacy of ayahuasca-assisted interventions for the treatment of alcohol use disorders. There is, however, considerable preliminary and supportive evidence derived from naturalistic, observational research, and structured information provided by healthy members of the general population and specific sub-populations.

Thomas et al. (2013) reported on outcomes for a small sample of people ($n = 12$) from a Coast Salish First Nation community in British Columbia, Canada who participated in a ceremonial ayahuasca-assisted intervention. All participants had been seeking treatment for substance use disorders, primarily alcohol and cocaine, and reported statistically significant improvements in measures of mental health and reductions in self-reported use of these substances at six-month follow-up. Argento et al. (2019a) reported on a qualitative analysis of participants' narrative of their experience and cited multiple aspects of the outcomes and potential mediating factors. Coinciding with the significant improvements in substance use and craving were the enhanced resolution of deeper, unresolved mental and emotional issues and trauma. Other factors cited in comparison with previous treatment experiences included enhanced connections with Spirit and nature, a heightened sense of self, and transformation in relationships with others.

A large-scale international survey (Lawn et al., 2017) showed that ayahuasca drinkers reported less problematic alcohol drinking than classic psychedelic users, although both groups reported greater problematic drinking than the other respondents. These results are consistent with studies of long-term frequent ayahuasca drinkers in the Brazilian syncretic churches, which consistently showed either complete remission or considerably reduced use among frequent ayahuasca drinkers based on the retrospective recall of lifetime alcohol or other drug use, including severe dependence (see Fábregas et al., 2010; Labate et al., 2010).

Using community surveys, Garcia-Romeu et al. (2019) explored the role of previous experience with psychedelics in cessation and reduction in alcohol consumption and problem drinking. They found psychedelic dosage, insight, mystical experiences, and personal meaning of experiences were associated with a significant reduction in alcohol use, controlling for prior alcohol consumption and related distress. Among those reporting the most significant declines in alcohol use and related problems, 28% cited changes in life priorities or values as facilitating their reduced alcohol intake.

Ketamine

Krupitsky and Grinenko (1997) reported an uncontrolled clinical study that compared two groups of patients who had received inpatient detoxification and a three-month residential program. One group received post-treatment follow-up as usual and the other received as-usual follow-up supplemented by one session of ketamine-assisted psychotherapy. They found the one-year

abstinence rates in the ketamine-assisted therapy group were 65.8% compared to 24% in the comparison group. The same paper reviewed relevant research from several years previous and postulated several underlying mechanisms based on their own work with over 1000 patients with alcohol use disorder.

Wong et al. (2015) completed a retrospective review of 23 patients who were hospitalized for management of severe alcohol withdrawal symptoms and who were administered ketamine as an adjunct to conventional treatment with benzodiazepines. They found a non-significant trend toward reduced benzodiazepine requirements at 12- and 24-hour post-ketamine initiation with medians of -40 and -13.3mg of diazepam equivalents.

Elias Dakwar at Columbia University Medical Center has become a leading expert in the assessment of therapeutic efficacy of ketamine for substance use disorders, including controlled trials focused on alcohol, cocaine and opioid use disorder and a study in the works focused on cannabis use disorder. Dakwar et al. (2020) reported on the effectiveness of a single-infusion of ketamine combined with a five-week outpatient regimen of motivational enhancement therapy for alcohol use disorder using a randomized midazolam-controlled pilot trial. Sample size was N = 40. Ketamine significantly increased the likelihood of abstinence, delayed the time to relapse, and reduced the likelihood of heavy drinking days compared to the control group. Secondary analysis showed that a mystical-type experience mediated the impact on at-risk drinking (Rothberg et al., 2021).

To investigate the safety and efficacy of ketamine compared to placebo for increasing abstinence in patients with alcohol use disorder, Grabski et al. (2022) conducted a proof-of-concept study that compared ketamine with mindfulness-based relapse prevention therapy to ketamine with alcohol education as a therapy control (n = 95, 35 women). Four groups were randomly assigned in this placebo-controlled, double-blind phase 2 clinical trial: (1) three weekly IV ketamine infusions (0.8mg/kg over 40 minutes) plus therapy, (2) three saline infusions plus therapy, (3) three ketamine infusions plus alcohol education, (4) three saline infusions plus alcohol education. The ketamine treatment was well-tolerated with no serious adverse events and was associated with more days of abstinence from alcohol at six-month follow-up compared to placebo. Confidence intervals were wide and there was no significant difference in rates of relapse between ketamine and placebo group, yet this study provides support for the benefits of psychological therapy with ketamine treatment as well as the tolerability of IV ketamine for adults with alcohol use disorder (Grabski et al., 2022).

Several other studies have explored the value of ketamine as a therapeutic agent for alcohol use disorders, including withdrawal management. A study by Yoon et al. (2019) reported that naltrexone followed by multiple ketamine infusions reduced alcohol cravings in patients with comorbid alcohol use disorder and depression. Das et al. (2019) found that ketamine infusions following alcohol consumption reduced reinforcing effects of alcohol and long-term drinking levels relative to those who received saline control.

Two published studies have focused on the role of ketamine in alcohol withdrawal and related comorbidities. Pizon et al. (2018) conducted a retrospective observational cohort study of 63 ICU patients admitted with delirium tremens and found that patients delivered ketamine infusion

after treatment according to guidelines for therapeutic use of benzodiazepines and phenobarbital were less likely to be intubated, had a decreased ICU stay by 2.83 days, and a trend toward overall reduced hospitalization.

Shah et al. (2018) evaluated the effect of adjunctive ketamine continuous infusion on symptom control and lorazepam infusion requirements for benzodiazepine-resistant, hospitalized alcohol withdrawal patients in the ICU. They conducted a retrospective review of patients receiving ketamine adjunctively with a lorazepam infusion for severe alcohol withdrawal between August 2012 and August 2014. Outcomes included time to symptom control, lorazepam infusion requirements, ketamine initial and maximum daily infusion rates, and adverse effects of ketamine (N = 30). All patients achieved initial symptom control within one hour of ketamine initiation. Median initial ketamine infusion rate was 0.75 mg/kg/h and the average maximum daily rate was 1.6 mg/kg/h. Significant decreases in lorazepam infusion rates from baseline were observed at 24h after ketamine initiation. No patients experienced documented CNS adverse effects. Two patients experienced hypertension and no patients experienced tachycardia related to ketamine. Authors suggested future studies to determine optimal dosing, timing of initiation, and place in therapy for benzodiazepine-resistant alcohol withdrawal. Interestingly, Niciu et al. (2015) observed that a family history of alcohol use disorder extended the antidepressant durability in individuals with a treatment history of depression.

There is a significant amount of research on the horizon concerning the role of ketamine in treatment and support for people with alcohol use disorder. McAndrew and colleagues (2017) have reported a proof-of-concept design for an RCT of ketamine as a therapeutic agent for the treatment of alcohol use disorder. This is a phase II, randomised, double-blind, placebo-controlled, parallel-group clinical trial taking place in two sites in the UK: the Southwest of England and London. Ninety-six recently detoxified alcoholics with comorbid depressive symptoms were to be randomised to one of four treatment arms with patients to receive either three sessions of ketamine (0.8 mg/kg administered IV over 40 minutes) or placebo (50 ml saline 0.9% IV over 40 minutes) plus either seven sessions of manualised psychological therapy or an alcohol education control. The planned primary endpoints are (1) relapse rates at 6 months and (2) percentage days abstinent at 6 months. Secondary endpoints include 3- and 6-month percentage days abstinent, tolerability (indicated by dropout), adverse events, depressive symptoms, craving and quality of life. Results have not yet been published.

4.1.3 Opioid Use Disorder

Classic psychedelics

The crisis of illicit drug toxicity, and particularly the penetration of fentanyl as an adulterant in street “heroin,” has been declared a public health emergency in both Canada and the United States. Rates of opioid-related deaths, paramedic and other first-responder calls, emergency department admissions and hospitalizations have further increased since the COVID-19 pandemic (Friedman & Akre, 2021; CCSA, 2020; Friesen et al., 2021). Few studies have investigated the relationship between opioid use and psychedelics, yet a small number of

surveys suggest interesting results. In a longitudinal cohort study of people who use drugs (n = 3813), Argento et al. (2022) conducted a survey among three harmonized prospective cohorts of people who use drugs in Vancouver, Canada. They found that of 3813 respondents, 229 (6%) used psychedelics in the past six months and that their psychedelic use predicted lower odds of daily opioid use over follow-up. Pisano et al. (2017) analyzed data from a large sample of illicit drug users in the USA who responded to the National Survey of Drug Use and Health (NSDUH) (2008–2013). They found that lifetime classic psychedelic use was associated with a 27% reduced risk of opioid dependence and 40% reduced risk of non-medical opioid use in the past year. Jones et al. (2022) sought to replicate and extend the Pisano et al. (2017) study using updated results from the NSDUH (n = 214505) to examine associations between use of classic psychedelics (psilocybin, LSD, peyote, mescaline) and OUD. Reported psilocybin use was associated with 30% lower odds of OUD, but no other psychedelic in the survey (LSD, peyote, mescaline) shared an association with OUD. Further, there was a significant association between lifetime psilocybin use and reduced odds of seven out of 11 DSM-IV criteria for opioid dependence and abuse. Based on this large-scale survey, psilocybin taken in a naturalistic context may have a protective effect for some diagnostic criteria related to OUD. However, these results are cross-sectional, correlational, and based on self-report, therefore no causal conclusions are possible. Jones et al. (2022) also highlight that the NSDUH does not include people experiencing homelessness, active-duty military members, or currently incarcerated people. They recommend that future research closely examine the impact of demographic factors on associations between psilocybin use and odds of OUD. Further, more research is needed to determine the differential relationship between the naturalistic use of various classic psychedelics (LSD, ayahuasca/DMT, peyote/mescaline, etc.) and mental health outcomes (Jones et al., 2022). See Section 4.6.7 on the potential health promotion/wellness potential of psychedelic use.

Ketamine

Two published studies have evaluated the efficacy of ketamine-assisted treatment for opioid use disorder. Krupitsky et al. (2002) conducted an RCT of 70 heroin-dependent participants in which they compared the efficacy of high dose ketamine vs. low dose ketamine in conjunction with psychotherapy. Abstinence rates at one month approached 85% in the high dose compared to 55% in the low dose group and were 24% at one year in the high dose group compared to 6% in the low dose group. Craving was also notably reduced in the high vs. low groups, with an enduring decline in craving noted pre-/post- infusion in the high dose group.

In a follow-up study, Krupitsky et al. (2007a) evaluated the efficacy of single vs. repeated sessions of ketamine-assisted psychotherapy in increasing abstinence from heroin. Participants were randomized to one or three sessions of ketamine given at one-month intervals. They found that 50% of subjects receiving multiple ketamine treatments were abstinent at one-year follow-up, compared to 22% of single-session treatments. They also noted significantly greater reductions in heroin craving in the repeated treatment group as compared to the single treatment group.

Jovaiša et al. (2006) conducted an RCT in which participants were given either saline placebo infusion or 0.5mg/kg/h of IV ketamine prior to rapid opioid antagonist induction under general anesthesia. Their results showed that ketamine could suppress physiologic response to opiate withdrawal. Mean arterial pressure, heart rate, and serum cortisol were significantly lower in the ketamine group during opioid antagonist induction under anesthesia. There were no significant group differences at four months on their secondary outcome measures of aftercare treatment retention, abstinence rates, self-reported health, or social/family life improvements, although both the placebo and ketamine groups were also started on opioid antagonist treatment. In their review of this literature, Jones et al. (2018) speculate that the lack of group differences may be related to initial opioid antagonist treatment in both groups or to administration of ketamine while the participants were unconscious.

Ibogaine

While there is a long history concerning the purported ability of a single dose of ibogaine to dramatically reduce drug use, including severe withdrawal symptoms, this is based largely on personal accounts, case studies, observational studies, and retrospective follow-up of participants in either formal ibogaine clinics in various countries or informal networks. This history, and the assessment of evidence that can be gleaned from it, is well-reviewed by Alper and Lotsof (2007) and Brown (2013). While the early history included the use of ibogaine for several substance use disorders, including alcohol, stimulant (cocaine), and opioid use disorder, more recent attention has turned to the role of ibogaine in the treatment of opioid use disorders, including but not limited to its role in blocking the signs and symptoms of opioid withdrawal. Although more focused in this sub-topic, the extant body of research is still comprised largely of observational research and case studies.

Cloutier-Gill et al. (2016) report a Canadian case of complete remission of severe opioid use disorder involving a 37-year-old female with a 19-year history of severe OUD. Following a four-day ibogaine retreat, she achieved an ongoing 18-month period of abstinence. Her previous longest period of continuous abstinence from opioids was two months while on methadone. No safety issues associated with ibogaine were observed in this case report (see below for general safety concerns). This case is not atypical of those reported in earlier research.

Several case studies have reported positive results of ibogaine treatment for opioid withdrawal, including a report on 32 patients treated at a clinic in St. Kitts (Mash et al., 2001) and another from 33 patients treated in non-medical settings (Alper et al., 1999). More recently, Mash (2018) reported on two follow-up observational studies, one based in Mexico (Brown & Alper, 2018) and the other in New Zealand (Noller et al., 2018). Noller and colleagues (2018) examined longitudinal treatment effects over a 12-month period among individuals receiving legal ibogaine treatment for opioid use disorder. A single ibogaine treatment reduced opioid withdrawal symptoms and achieved opioid cessation or sustained reduced use in dependent individuals as measured over 12 months. The Mexico-based follow-up study by Brown and Alper (2018) reported outcome measures following opioid detoxification with ibogaine in 30 patient volunteers. Subjective Opioid Withdrawal Scale (SOWS) scores and Composite Addiction Severity Index Scores (ASIC) were used to track long-term benefit at 1, 3, 6, and 12-months

post-treatment follow-up interviews. SOWS scores decreased significantly and at one-month posttreatment follow-up 15 subjects (50%) reported no opioid use during the previous 30 days. Drug Use and Legal and Family/Social Status scores were improved relative to pre-treatment baseline at all posttreatment time points. Improvement in Drug Use scores was maximal at one month, and subsequently sustained from 3 to 12 months at levels that did not reach equivalence to the effect at one month.

One patient enrolled in the New Zealand study experienced a serious cardiac-related adverse event of a type that has been reported on several occasions in the ibogaine literature and which has significantly stalled clinical research on this medication (Alper, 2001; Meisner et al., 2016). Pre-existing conditions, especially cardiac-related conditions, have been found to underpin most recorded deaths associated with ibogaine treatment for opioid use or other substance use disorder. Of particular concern is the dosage level required to achieve certain therapeutic effects as well as the underground, unregulated nature of ibogaine practitioners. To ensure safety of use, recent work has been undertaken to better estimate a safe dosage (Schep et al., 2016). These and other safety-related concerns, as well as high research costs, have inhibited ibogaine research from progressing to randomized control trials (Alper et al., 2012). Argento et al. (2019b) make an eloquent case that, in the context of the current epidemic of illicit drug poisonings and overdoses, exacerbated by the COVID-19 pandemic, that we in Canada should be exploring all innovative treatments and that the evidence for ibogaine and opioid withdrawal is strong enough to reopen that door for further research.

4.1.4 Cocaine Use Disorder

Ketamine

Dakwar et al. (2014b) implemented a three-arm cross-over trial with a small sample ($N = 8$) and determined that ketamine may have efficacy in treating problematic cocaine use. They found that ketamine was associated with increased motivation to quit cocaine compared to lorazepam and also reduced cocaine craving. Although there was no placebo comparison, there was a significant reduction in frequency of use (22 days of use/28 days at baseline vs. 5/28 days at 4-week follow-up) as well as the amount of money spent on cocaine in the follow-up period (\$149.30/use day at baseline vs. \$10.50/use day at 4-week follow-up). Results also highlighted the importance of the mystical-type experience in mediating the positive outcomes. In a related follow-up study of 20 non-treatment seeking cocaine dependent participants, Dakwar et al. (2017) conducted a cross-over design, inpatient laboratory paradigm trial evaluating the efficacy of a single infusion of 0.71mg/kg ketamine with 0.025 mg/kg midazolam as the active control. Sample size was $N = 20$. During a six-day hospitalization for the experimental medication infusions, subjects participated in “choice sessions” (during which they could elect to self-administer 25mg cocaine or receive a cash payment of \$11). Rates of cocaine self-administration were reduced by 66% relative to pre-infusion baseline choice rates with no significant pre-/post changes in preferences among the control group. Another controlled trial from the same lab found that study subjects with cocaine dependence who received a single subanesthetic infusion of ketamine as they initiated mindfulness-based relapse prevention had a

significantly greater likelihood of end-of-study abstinence compared with those who received midazolam (Dakwar et al., 2019).

Ibogaine

In Brazil, a combined approach of psychotherapy and ibogaine—which is unregulated in that country—has been studied for treating substance use disorders. Schenberg et al. (2014) conducted a retrospective analysis of data from 75 previous cocaine and crack, alcohol, and cannabis users (72% poly-drug users). They observed no serious adverse reactions or fatalities and found 61% of participants abstinent. Participants treated with one ibogaine experience reported abstinence for a median of 5.5 months and those treated multiple times reported abstinence for a median of 8.4 months. Both single and multiple treatments led to longer abstinence periods than before the first ibogaine session.

Ayahuasca

A Brazilian observational study examined the benefits of ayahuasca for improving addiction to crack cocaine. Cruz and Nappo (2018) conducted in-depth qualitative interviews with a purposeful sample of 40 crack cocaine users consuming the ayahuasca admixture in a religious context. Participants reported that ayahuasca allowed them to access a dimension of consciousness which enabled them to solve problems and traumas and to reduce consumption of crack cocaine. The religious ceremony was said to have increased participants' spirituality, and the reception from the community was reported to have given them a sense of self-esteem, strengthening them emotionally and socially. The positive experience had been incorporated into the daily routine of most participants. The authors suggest that ayahuasca drinking in a religious context may have therapeutic value for treatment of dependence on crack cocaine.

4.1.5 Cannabis Use Disorder

Azhari et al. (2021) found that ketamine infusion (0.71 mg/kg or 0.41 mg/kg) + MET/MBRP significantly decreased cannabis use compared to baseline and significantly increased participants' confidence in their ability to abstain from cannabis use during triggering situations.

4.1.6 Psychedelics for Substance Use Disorders: Summary

Recent research reviews focusing on psychedelics and substance use disorders typically conclude with cautious optimism regarding research efficacy, but also decry the lack of randomized controlled trials, especially those that are well-blinded and with sufficient sample size to detect clinically meaningful group differences.

To summarize, the general picture that emerges from the research on psychedelic-assisted treatment for substance use disorders is one of considerable promise and the call for more research. Clearly there is sufficient evidence to warrant further investigation, especially given the high percentage of people who do not respond well to current treatment alternatives and in

the face of the global burden of substance use disorders, including the current illicit drug poisoning epidemic. Promising and consistent results have come from some controlled studies, albeit with small sample sizes and/or proof of concept designs. Such studies have been conducted to examine psilocybin and tobacco use disorder; LSD and alcohol use disorder; and ketamine for cocaine use disorders, cannabis use disorders, and opioid withdrawal, either alone or in combination with other therapeutic agents or practices.

Naturalistic observational studies with ayahuasca and cross-sectional research with healthy individuals in the community also lend important information to a promising picture. The largely underground work with ibogaine and opioid withdrawal is also worthy of focused attention and appears to hold promise, although any future protocol for research will have to include extensive screening and risk management procedures. In short, the arguments to rejuvenate this research domain have been cogent and cautiously optimistic with respect to substance use disorders, an opinion shared by some of Canada's leading substance use researchers (Argento et al., 2019a; Tupper et al., 2015).

4.2 Outcomes Related to Depressive Disorders

4.2.1 Major Depressive Disorder (MDD) and Suicidal Ideation

Worldwide, nearly 300 million people are affected by depression, making it the most prevalent cause of disability in the world and, after anxiety, the second most common psychiatric disorder in adults (Bahji et al., 2021; Gupta et al., 2021). In Canada, major depressive disorder (MDD) has an estimated national prevalence of 4.72%, making it the most common mental disorder (Palay et al., 2019). The economic burden of depressive disorders in the United States was estimated at \$210.5 billion in 2010 (Chow et al., 2019), primarily due to significant healthcare resource use and reduced workplace productivity.

Currently approved antidepressant medications provide relief for some individuals within several weeks of starting treatment. However, it is estimated that 1/3 of affected individuals will not achieve symptom attenuation with conventional medications (Bahji et al., 2021). Individuals that do not have a response to medications after at least two routine antidepressants are referred to as experiencing 'treatment resistant' depression (TRD) (Souery et al., 2006). Current medications for major depressive disorder (MDD) are based on the monoamine hypothesis of depression pathophysiology, where levels of certain neurotransmitters (serotonin and norepinephrine) are lower than normal, leading to a lack of neural excitement (Papakostas et al., 2020). Alternatively, the 'neurotrophic hypothesis' suggests a reduction in nerve growth factors is responsible for the decrease in neuroplasticity and neurogenesis associated with depression (Groves, 2007). Glutamatergic neurotransmission may also be implicated in depression, where low levels of glutamate are responsible for depressive symptoms (Grabski et al., 2020; Papakostas et al., 2020). Ambiguity in the etiology and pathophysiology of depression complicates treatment options for affected individuals.

Ketamine

Racemic ketamine is not approved by Health Canada or the US FDA for any psychiatric disorder, but there is significant and increasing off-label use by clinicians for depression. Intranasal esketamine (Spravato®) is approved by Health Canada, the US FDA, and the European Medicines Agency (EMA) for patients with treatment-resistant depression (TRD). In 2016 the Canadian Network for Mood and Anxiety Treatments (CANMAT) listed IV ketamine (i.e. racemic ketamine) as an experimental treatment due to the limited evidence available for its efficacy. To update its guidelines, a CANMAT task force conducted a systematic review of the safety and efficacy of racemic ketamine among publications in French and English (Swainson et al., 2021). Intranasal ketamine (i.e., esketamine) and IV esketamine were excluded from the search terms since IN esketamine in the form of Spravato® is already approved for medical use and clinical research has demonstrated that IV ketamine is noninferior to IV esketamine. The CANMAT task force concluded that there is Level 1 (highest rating for rigor) evidence for the efficacy of a single infusion of IV ketamine as an antidepressant, particularly novel for its antisuicidal effects (Swainson et al., 2021). However, there is only Level 3 evidence for repeated infusions and Level 4 evidence for relapse prevention, indicating the need for more clinical studies. These promising yet mixed results led the task force to consider IV ketamine as a third-line recommendation for adults with TRD. Further, they did not find sufficient evidence to recommend IV ketamine for pediatric or geriatric populations, also indicating the need for clinical research (Swainson et al., 2021). It is notable that there was no mention in the CANMAT report concerning the use of psychotherapeutic support or of ketamine-assisted psychotherapy as part of clinical recommendations.

Ketamine, a glutamatergic modulator and N-methyl-d-aspartate (NMDA) receptor antagonist, is thought to increase prefrontal extracellular glutamate, thus treatment success with ketamine seems to support the glutamatergic neurotransmission hypothesis of depression (Grabski et al., 2020). Evans et al. (2018) used fMRI data among unmedicated MDD patients (n = 33) and healthy controls (n = 25) to investigate the effect of a single IV infusion of ketamine (0.5mg/kg) on the default mode network (DMN) at two- and 10-days follow-up. This double-blind, placebo-controlled crossover study (n = 58) found that ketamine may normalize the interaction between salience networks and the DMN among patients with MDD, which the authors suggest is supportive of the triple network disfunction model of MDD (Evans et al., 2018).

In a 2014 systematic review and meta-analysis, Fond et al. (2014) reported that ketamine, on its own and combined with other medications, is effective for rapid treatment of unipolar and bipolar depression. Another review of seven RCTs, which used saline or midazolam as controls, found a range of 37%-71% ketamine response rate (RR = at least 50% reduction in depression ratings) (Rasmussen, 2016).

Sanacora et al. (2017), reviewing seven published, placebo-controlled, double-blind randomized clinical trials on intravenous (IV) ketamine hydrochloride indicated that ketamine is useful as a treatment for MDD episodes without psychotic features. However, noted limitations include: benefits were only assessed during the first week after one dose of IV ketamine and that antidepressant effects were short-lived, although they acknowledge that emerging studies

suggest that repeated dosing can extend the duration of effect for several weeks. Similarly, in a systematic review of 17 studies (n = 739, 54% female, mean age 44) that focused on treatment of depression or a combination of depression with other mental disorders with ketamine, outcomes were assessed from within the first 24 hours to within two weeks and only four studies assessed outcomes more than two weeks post-treatment (Grabski et al., 2020). The same authors indicated that psychoactive effects were most often assessed just before and one hour after treatment, while two studies in their review assessed psychoactive effects at four hours post-administration (Grabski et al., 2020).

Grabski et al. (2020) determined that 20% of the 33 relationships examined in their systematic review were significant. Thus, the authors feel the association between ketamine's acute psychoactive effects and psychiatric treatment outcomes is 'inconclusive'. A meta-analysis could not be completed in this review due to the heterogeneity of the studies (Grabski et al., 2020). Bahji et al. (2021) conducted a systematic review of 24 RCTs (n = 1877) treating individuals with ketamine/esketamine for TRD. The authors concurred that proof of efficacy for ketamine remains low and encouraged more RCTs with sufficient power to explore the efficacy and safety issues associated with its administration. They acknowledged that, for very short-term use, ketamine is capable of reducing depressive symptoms rapidly after administration, with effects lasting up to seven days after a single dose. They also suggest that IV ketamine as opposed to intranasal (IN) esketamine should be used for TRD (Bahji et al., 2021). A limitation of this review was the varying definition of TRD amongst studies, an issue that is discussed below.

In a meta-analysis of 20 RCTs investigating the efficacy of ketamine on TRD, Kryst et al. (2020) found the largest effect size of ketamine vs. controls in significantly reducing depressive symptoms to occur at 24 hours post infusion. While ketamine on its own showed no significant difference from control at seven days post-infusion, significant reductions in depression severity scores were seen after two to three weeks of repeated ketamine treatment (Kryst et al., 2020). A systematic review of five studies (three RCTs, two open-label studies, n = 110) revealed that depression symptoms, suicidal ideation, and anhedonia improved after one infusion of ketamine (Joseph et al., 2021). In a review representing 147 participants, rapid, transient antidepressant effects occurred with short psychotomimetic and dissociative effects (Newport et al., 2015).

Maguire et al. (2021) indicated that combinations of esketamine with oral antidepressants induced clinical relief in depressive symptoms in the majority of patients receiving esketamine. Papakostas et al. (2020) indicated that esketamine was significantly more effective than placebo augmentation for MADRS (Montgomery-Asberg Depression Rating Scale) score change. Kryst et al. (2020) reported that ketamine combined with ongoing antidepressant treatment showed a significant difference compared to control, which was present up to seven days post-infusion. In the same study participants showed improvements in the Hamilton Depression Rating Scale (HDRS) and MADRS (Kryst et al., 2020). Another recent systematic review showed that racemic ketamine, compared to esketamine, demonstrated greater overall improvement rates (Cavenaghi et al., 2021).

Ochs-Ross et al. (2020) in a Phase 3, double-blind study examined the effect of adjunctive IN esketamine with SSRI/SNRI antidepressants in people 65 years and over ($n = 138$). Both the control group and treatment group began a new antidepressant and then received either IN esketamine or placebo. Although there were no statistically significant results, esketamine reduced the depression severity by 5.3 times compared with placebo and, in those less than 75 years old, symptoms improved faster as did remission rates (Ochs-Ross et al., 2020).

As mentioned, an important limitation identified in reviews of ketamine studies is the lack of consistency in how TRD is defined (Bahji et al., 2021; Grabski et al., 2020; McIntyre et al., 2020). Examples of ambiguity in the definition of treatment resistance from a review of 17 studies were (Grabski et al., 2020):

- A minimum requirement of ineffective antidepressant trials ranging from one to four
- Whether the antidepressant had to have been prescribed during the episode
- Whether the drugs had to be from different classes
- Whether treatment with a non-pharmacological method must have been attempted

Standardizing the definition of treatment resistant depression is important for establishing consistency across clinical trials. Further, esketamine (Spravato™) was approved for use in TRD by the FDA and EMA and without a consistent definition of TRD it will be difficult to know who is best suited to receive it (Grabski et al., 2020). The results of a 2020 meta-analysis to evaluate effect sizes across routes of delivery and formulations of ketamine support the short-term efficacy of IV (racemic, esketamine), IN (racemic, esketamine), and oral (racemic) ketamine formulations in adults with TRD, although studies of oral ketamine need larger samples across independent sites (McIntyre et al., 2020). However, no conclusions regarding comparative efficacy of the different formulations and routes of delivery could be made because studies were heterogeneous with respect to sample composition, illness characteristics, and definitions of TRD, among others (McIntyre et al., 2020).

The typical dose of ketamine for relieving depression and bipolar depression with prominent anhedonia reported in systematic reviews and meta-analyses is 0.5 mg/kg per 40 min IV infusion (Gałuszko-Węgielnik et al., 2019; Grabski et al., 2020; Sanacora et al., 2017). Limitations of this dosing regimen are that it requires multiple infusions per week and repeated insertions of the infusion pump (Grabski et al., 2020; Papakostas et al., 2020). Despite this being the typical route and dose of ketamine, Sanacora et al. (2017) concluded that there is limited information regarding different routes and doses that may be viable alternatives to ameliorate said limitations. Their meta-analysis included six trials assessing the standard dose and three trials assessing very low doses of ketamine hydrochloride (50 mcg IN spray, 0.1-0.4 mg/kg IV, and 0.1-0.5 mg/kg IV, IM or SC). The standard dose was found to be more effective than very low doses in reducing depression severity (Sanacora et al., 2017). Due to heterogeneity in trial designs and small sample sizes, the authors were unable to provide meaningful analysis of alternative doses or routes of administration compared to the standard dose (Sanacora et al., 2017). For patients with a body mass index (BMI) of 30 or higher, these same authors recommend that ketamine should be given based on ideal body weight, as

hemodynamic changes were seen in these individuals when standard ketamine dose was used. However, they concede that information on this topic is limited.

The bioavailability of intranasal ketamine at 45-50% across different racial and age groups is higher than oral, sublingual, and rectal delivery methods (Papakostas et al., 2020). However, IV ketamine, compared to IN esketamine, showed more significant response and remission rates, and had lower drop-outs due to unwanted events (Bahji et al., 2021). In the same study, parallel trials demonstrated more significant improvements in depression rating scores while crossover trials showed higher response and remission rates (Bahji et al., 2021). McIntyre et al. (2020) discussed that effect-size was greatest for IV ketamine (typically single infusion studies) at 2–6 days post-infusion while for IN esketamine it was greatest at 24 hr post-infusion (typically repeat-dose studies and often with added antidepressant). Thus, interpretation is difficult due to different dose schedules. Interestingly, oral ketamine demonstrated efficacy at 21-28 days and the benefits from the oral route may be more apparent with multiple doses across a number of weeks, perhaps due to increased bioavailability (McIntyre et al., 2020).

The use of subcutaneous (SC) ketamine has been explored primarily for pain (Backonja et al., 1994; Mercadante et al., 1995; Weber et al., 1975), perioperative analgesia (Gurnani et al., 1994; Javid et al., 2012; McDowell et al., 2018), and anesthesia (Cavenaghi et al., 2021). A systematic review examining efficacy and tolerability of SC ketamine in depression found heterogeneous methods amongst the few relevant studies, thus a meta-analysis was not feasible (Cavenaghi et al., 2021). Of the 12 articles included, two were RCTs, five were retrospective, and five were case reports. Available data suggest that SC ketamine and esketamine are promising alternatives for TRD, showing comparable efficacy and short-term side effects to IV ketamine. Additionally, lower doses than usual resulted in depression relief, which may be highly important for those vulnerable to side effects, such as the elderly and those with comorbidities (Cavenaghi et al., 2021). Limitations of the studies included in this review were small sample sizes and some patients were drawn from the same sample (Cavenaghi et al., 2021).

George et al. (2017) in their RCT of ketamine for TRD in adults over age 60 (the majority having co-morbid anxiety and/or physical illness), found that ketamine given subcutaneously in single doses was "effective, safe and well-tolerated". Of those who completed, 68.8 % achieved remission at one point and 50% had remission lasting seven days post-treatment. In a systematic review by Gill et al. (2020) examining the effects of ketamine on cognition in TRD, the authors note that few significant cognitive benefits were observed but also noted that impairments were also minimal, demonstrating the safety of ketamine (Gill et al., 2021). Five studies totalling 157 participants (2 open-label and 3 RCTs) were included and all patients must have had shown insufficient response to at least two antidepressants. The range of IV ketamine dosing was 0.2mg/kg to 0.5mg/kg among the five studies. Two studies found that reduced neurocognitive performance was associated with better response to ketamine. Another study found statistically significant improvements in memory (working, visual and complex working) after the sixth infusion compared to baseline. Improvements in working memory and processing speed were seen in those with anxious TRD in another study. The final study demonstrated improvements in attention and response but only with 0.5mg/kg dosage (Gill et al., 2021).

Ketamine combined with ECT for depression

McGirr et al. (2015) carried out a systematic review of five RCTs (n = 182) to determine the efficacy and tolerability of administering ketamine combined with electroconvulsive therapy (ECT) for major depressive disorder (MDD). Two of the studies included a mixed unipolar and bipolar depression sample and another included people with TRD. Study designs differed, with three RCTs having six ECT sessions, one with a single ECT session and the remaining had variable ECT depending on subject. IV ketamine dosages varied from 0.4mg/kg to 1-2mg/kg and electrode placement differed among the five studies as well. McGirr et al. (2015) concluded that combining ketamine with ECT shows a lack of efficacy and suggest that more research is needed in this area.

Huang et al. (2020) reported on a clinical trial to examine if serum changes in brain-derived neurotrophic factor (BDNF) are the result of ketofol (ketamine-propofol combination) when used with ECT for clients with TRD. Thirty healthy adults with MDD experiencing an acute episode who were not prescribed antidepressants or antipsychotics during the period of the study were included. Ketofol at 1.0 mg/kg was given prior to 8 ECT sessions. The Hamilton Depression Rating Scale (HAMD-17) and the Brief Psychiatric Rating Scale (BPRS) were used to monitor symptoms and ELISA was used to measure serum levels of BDNF at baseline and after ECT sessions 2, 4, and 8. Serum levels of BDNF were also collected from 30 healthy controls. Sixteen subjects achieved remission, but all subjects responded to the treatment with a significant reduction in depression and psychotic symptoms after ECT. However, serum level differences were not significant between those who had remission and those who did not and there was no significant correlation between BDNF levels on either the HAMD-17 or the BPRS. The authors suggest that similar studies, with more people, are needed to validate findings and improve generalizability (Huang et al., 2020).

In a more recent systematic review of six studies (three blind RCTs and three open-label studies) comparing ketamine treatment with ECT for TRD, no definitive answer was found regarding whether ketamine treatment was an appropriate substitute to ECT for TRD. One of three RCTs showed greater improvement with ketamine whereas the two others found no significant difference. The authors also noted that although ketamine treatment resulted in faster antidepressant effects, these changes were not as long-lasting compared to ECT. However, they noted that ketamine had a 'more favourable neurocognitive side effect profile' as compared to ECT (Veraart et al., 2021).

A 2020 review of currently registered clinical trials using ketamine found that the majority of trials (70%) were investigating ketamine for mood disorders (unipolar: 60%, bipolar: 0.7%, both: 5.7%), while suicidal ideation (13.1%), PTSD (5.4%), and OCD (3.6%) were also being studied (Peyrovian et al., 2020). IV administration was the most common (87%) and 50% of IV ketamine studies relied on a single dose.

Esketamine as a treatment for depression was approved by the FDA and came to market in the U.S. for treatment of depression in 2019 and is currently under review for this indication by Health Canada.

Ayahuasca

Osório et al. (2015) reported results from an open label trial in which ayahuasca was administered to six patients (two men, four women, with an average age of 44.16) with recurrent MDD in an inpatient psychiatric unit in Brazil. Statistically significant reductions (up to 82%) in depressive scores were observed at one, seven, and 21 days after ayahuasca. Results suggested that ayahuasca has rapid anxiolytic and antidepressant effects in patients with a depressive disorder. Given the average two-week wait time for the therapeutic onset of antidepressant medications, the authors note that ayahuasca may provide faster reductions in depressive symptoms. Ayahuasca was well tolerated by all patients, suggesting safety in its use with depressed patients. Vomiting (50% of subjects) was the only adverse experience reported in this trial. It should be noted that nausea and vomiting are common effects of drinking ayahuasca, and in many traditional contexts vomiting is considered desirable as part of the healing process (Politi et al., 2021). Thus, while the studies discussed here report this as an 'adverse experience', purging may indeed play a role in the therapeutic process (Fotiou & Gearin, 2019). Osório et al. (2015) note their findings to be consistent with earlier studies reporting good tolerability and safety when ayahuasca was administered to healthy volunteers. This early open-label trial is characterized by important limitations, including small sample size, the absence of a robust inquiry into adverse effects, and the lack of placebo and control groups. Nevertheless, it was the first modern-era clinical trial investigating the therapeutic application of ayahuasca for a psychiatric condition. Observational and longitudinal studies have been completed among ayahuasca church members demonstrating no long-term adverse effects and comparative improvements in substance use and other psychiatric symptomology (Bouso et al., 2012; McKenna, 2004).

Sanches et al. (2016) report rapid and persisting antidepressant effects from a single dose of ayahuasca (2.2mL/kg) in patients with recurrent depression. Seventeen volunteers (14 women, 3 men with a mean age of 42.71 years) with recurrent MDD participated in the study. Of the participants, thirteen were experiencing a current moderate episode, three a mild depressive episode, and one a severe depressive episode. Volunteers underwent single-photon emission computerized tomography (SPECT) imaging. Patients were evaluated with the HDRS, MADRS, the Brief Psychiatric Rating Scale, the Young Mania Rating Scale, and the Clinician Administered Dissociative States Scale during acute ayahuasca effects and at one, seven, fourteen, and finally at twenty-one days after drug intake. Sanches et al. (2016) found ayahuasca administration was associated with increased psycho-activity and significant decreases in depression-related scores from 80 minutes to day 21. Results were consistent across all volunteers regardless of current depressive episode. Volunteers experienced significant score decreases in depressed mood, sadness, anxiety, feelings of guilt, suicidal ideation, difficulties at work/activities, pessimistic thinking, and difficulty concentrating. Improvements in blunted affect and emotional withdrawal were also observed.

SPECT imaging showed increased blood perfusion in the left nucleus accumbens, right insula and left subgenual area after ayahuasca intake. Some imaging results may be specific to depressive patients. These brain regions are implicated in the regulation of mood and emotion. Ayahuasca was well tolerated and peak psychoactivity was noted at 40-80 minutes. Vomiting

was the only adverse effect recorded (47%). It is important to note that in this study, a diagnosis of bipolar disorder and a previous history of mania or hypomania induced by antidepressant or substance use were all considered exclusion criteria. The authors note that ayahuasca may be contraindicated for bipolar disorder, citing a case study in which a bipolar individual experienced significant mania resulting from ayahuasca ingestion (Sanches et al., 2016).

Study results suggest that ayahuasca may have fast-acting and sustained antidepressant properties. Treatment was not randomized or double-blinded, and there was no placebo or other comparator group involved, so it is difficult to conclude that observed changes were indeed caused by ayahuasca. While these trials are small and open-label, they do indicate promising potential efficacy in a novel and fast-onset approach to treating depression.

Building on the earlier open-label trials, Palhano-Fontes et al. (2018) conducted a parallel-arm, double-blind randomized placebo-controlled ayahuasca trial in twenty-nine patients (eight men, twenty-one women, mean age of 42) with TRD. Patients received a single dose of either ayahuasca or placebo within the clinical setting of a university hospital in Brazil. Changes in depression severity were measured with the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hamilton Depression Rating scale. Significant antidepressant effects of ayahuasca were noted when compared with placebo at all-time points (days one, two, and seven after dosing). Depression scores were significantly lower in the ayahuasca group compared with placebo at day one and at day two. Between-group effect sizes increased from day one to day seven. Improvement rates were high for both groups at days one and two, and significantly higher in the ayahuasca group at day seven (64% v. 27%). Remission rate showed a trend toward significance at day seven (36% v. 7%). No serious adverse events were observed during or after dosing, and all patients reported feeling safe. The most common adverse effect was nausea, with 57% of participants vomiting. Some patients reported acute psychological distress during the acute effects of ayahuasca.

This study provides new and additional evidence supporting the safety and therapeutic value of ayahuasca, provided within an appropriate clinical setting, to help treat depression. The authors do note the potential for a high placebo effect given the supportive care provided to both control and trial groups. Larger trial populations are needed, and the difficulty in blinding creates risk of bias. Further, this trial was limited to patients with TRD with a long course of illness and high comorbid personality disorder, precluding a generalization of these results to all classes of depression.

This trial is reported as the first controlled trial to test a psychedelic for TRD. Its parallel-arm, double-blind, randomized, placebo-controlled trial design gives it a level of methodological rigor to help interpret results. Larger multi-site RCTs with longer follow-up periods and more attention to the role of set and setting are indicated to establish the efficacy of ayahuasca in treating any form of depression. Nevertheless, these three early trial results indicate promise in the treatment of depression using ayahuasca for some types of patients, and ayahuasca may be unique in its rapid onset of anxiolytic and antidepressant effects.

In addition to this small number of clinical studies of depressed patients, other investigators have reported depression-related outcomes before and after the use of ayahuasca in

naturalistic, often ritualistic, contexts. Jiménez-Garrido et al. (2020) studied the effects of ayahuasca on mental health, including depression, in samples drawn from shamanic ceremonial groups, syncretic ayahuasca churches, and a third group who had drunk ayahuasca in a psychotherapeutic context. The focus was on comparing ayahuasca-naïve participants (i.e., first time users) and experienced (long-term) users. Among first-time users, 80% of participants showed significant pre-post reductions in depression as measured by the Hamilton Depression Rating Scale, which persisted for six months or longer. Longer-term users showed lower depression scores compared to the naïve participants.

Other studies of ayahuasca use within naturalistic contexts (Barbosa et al., 2009; Kaasik & Kreegipuu, 2020; Kiraga et al., 2021; Uthaug et al., 2021b) including large scale survey samples (Ona et al., 2019; Perkins et al., 2021; Sarris et al., 2021) have focused on psychiatric symptoms related to depression and anxiety and wide range of measures of overall mental health and well-being. These are summarized in section 4.6.7 below. Taken together this body of work in naturalistic settings complements and points in the same promising direction as the results of the few but well-designed clinical studies.

Psilocybin

The first small-scale feasibility trial on psilocybin for depression was an open-label, single-arm pilot study with no control group reported by Carhart-Harris et al. (2016a). 12 patients (6 female, 6 male) with moderate-to-severe treatment-resistant unipolar depression each received two doses of psilocybin (10mg and 25mg) seven days apart. Psychological support was provided before, during, and after each dosing session. Depressive symptoms were assessed from one week to three months post-treatment using the Quick Inventory of Depressive Symptoms (QIDS) as the primary efficacy measurement. Feasibility was measured by patient-reported intensity of effect.

Psilocybin was well tolerated by all patients and no serious adverse events were observed. Adverse reactions documented included transient anxiety during drug onset (n = 12), transient confusion (n = 9), mild nausea (n = 4), and transient headaches (n = 4). Psilocybin acute effects were observable after 30-60 minutes of dosing, peaked at 2-3 hours, and were negligible by six hours after dosing. Depressive symptoms were markedly reduced at one week and three months after the high-dose treatment session. The response rate was 67% (n = 8) one week after treatment (HAM-D and BDI), with seven of these eight patients also meeting criteria for remission. 58% (n = 7) of the trial subjects maintained their response for three months, and 42% (n = 5) remained in remission, suggesting sustained and persisting effects. Marked and sustained improvements in both anxiety and anhedonia were also observed. Data suggested further research is warranted.

Limitations to this study were a small sample size and demonstrated possible expectancy bias, with significant suggestibility also noted. It is unknown how the preparatory session (four hours pre-treatment) provided by study psychiatrists may also have contributed to outcomes. The role of the setting was also described as significant, as study subjects reclined in a comfortable position for the psilocybin dosing sessions, listened to a curated playlist of music with high-

quality sound and earphones, and were always accompanied by two psychiatrists. Therapists were non-directive but could provide support and checked in with patients at pre-set intervals. Debriefing (integration) was provided at one-week follow-up. This study provided preliminary support for the safety, feasibility, and efficacy of psilocybin-assisted therapy for TRD and laid the groundwork for subsequent RCTs. The authors concluded that, with appropriate safeguards and a supportive setting, psilocybin can be safely administered to this patient group.

Carhart-Harris et al. (2018a) would later provide updated and extended assessment of outcomes with six-month follow-up on 20 (6 female) patients with TRD treated with psilocybin. This six-month follow-up included eight additional patients added to the original cohort of 12 reported in 2016 in an open-label feasibility trial involving two oral doses (10mg and 25mg) administered seven days apart. The primary outcome was change in severity of self-reported depressive symptoms (Quick Inventory of Depressive Symptoms, QIDS-SR16) at 1, 3, and 5 weeks, as well as 3- and 6-months post-treatment. Five weeks was considered the primary endpoint. Secondary measures included the Beck Depression Index, STAI (anxiety) ratings, SHAPS (anhedonia), HAM-D (depression) and GAF (global functioning). The main criteria for inclusion in the trial were unipolar major depression of at least moderate severity with no improvement despite at least two courses of different antidepressant medications for a six-week minimum within the current depressive episode. Exclusion criteria included: current or previously diagnosed psychotic disorder or an immediate family member with a diagnosed psychotic disorder. Preparation via psychological support, acute support during session, and post-session integration support were all provided.

A rapid and sustained response above what would be expected from placebo was observed in many patients. Most notably, all 19 patients who completed the trial showed some reductions in the primary outcomes at one-week post-treatment, with (nominally) maximal effects demonstrated at five weeks. Safety was again maintained, and a sizeable portion of the group demonstrated benefit on a persisting basis. Suicidality scores were significantly reduced one- and two-weeks post-treatment. Consistent with the report on outcomes from the 12 patients from the previous initial feasibility trial (Carhart-Harris et al. 2016a), no severe adverse experiences were documented, and the treatment was generally well-tolerated. The most common adverse effects were transient anxiety lasting for minutes ($n = 15$) and headaches lasting for no more than 1-2 days ($n = 8$). Five patients reported transient nausea and three reported transient paranoia.

Conclusions on efficacy are limited by the absence of a control group and lack of attention to set and setting, the open-label design, and the lack of diversity in the trial cohort. Nevertheless, with these caveats, results suggest proof-of-principle. Further, the authors suggest an additional exclusion criterion for future psilocybin trials to include psychiatric conditions incompatible with establishment of therapeutic rapport and/or safe exposure to psilocybin, such as suspected borderline personality disorder.

Going beyond this early proof-of-principle trial which established safety and tolerability and highlighted the relatively quick onset of anti-depressant effects due to treatment with psilocybin, the authors would next trial psilocybin in direct comparison to treatment with escitalopram

(Carhart-Harris et al., 2021). In this six-week, phase two, double-blind, randomized, controlled trial involving patients with long-standing, moderate-to-severe major depressive disorder, psilocybin was compared with the selective-serotonin reuptake inhibitor escitalopram over a six-week period. Patients received either two separate doses of 25 mg of psilocybin two weeks apart plus six weeks of daily placebo (psilocybin group) or two separate doses of one mg of psilocybin three weeks apart plus six weeks of daily oral escitalopram (escitalopram group). All patients received psychological support. The primary outcome measure was change from baseline in the score on the 16-item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR-16) along with 16 secondary outcomes. A total of 59 (average age of 41, 35% female) patients were enrolled in the study; 30 were assigned to the psilocybin group and 29 to the escitalopram group. Trial results did not demonstrate significant difference in antidepressant effects between psilocybin and escitalopram in this selected group of patients. Mean change from baseline in QIDS-SR-16 at week six showed no statistical difference between trial groups.

Secondary outcomes generally favoured psilocybin, but the analyses of secondary outcomes lacked confidence and correction for multiple comparisons. QIDS-SR-16 response at six weeks occurred in 21 patients (70%) in the psilocybin group and in 14 patients (48%) in the escitalopram group (difference, 22 percentage points; 95% CI) and QIDS-SR-16 remission at week six occurred in 17 patients (57%) in the psilocybin group and in eight patients (28%) in the escitalopram group (difference, 28.1 percentage points; 95% CI). No conclusions can be drawn from this data.

No serious adverse events were observed in either trial group, and any psilocybin-related adverse experiences typically resolved within 24 hours after dosing. Headache and nausea were most common. No changes in visual perceptual phenomenon, psychotic-symptoms or dependency-related behavior were found at six-week follow up. In both trial groups, depression scores at week six were lower than baseline scores. However, the absence of a control condition limits the ability to assign conclusions about the effect of either trial agent alone. Incidence of adverse events was comparable between the trial groups, though the percentages of patients who experienced anxiety, dry mouth, sexual dysfunction, or reduced emotional responsiveness were higher in the escitalopram group than with psilocybin. One clear limitation of this trial is the brief duration of escitalopram treatment provided, given its delayed onset of antidepressant effects. Further, the trial lacked diversity in its patient population, limiting the generalizability of results. As in the previous trial, the lack of attention to the contribution of the psychological support component also challenges interpretation. Considering the difficulty in blinding to the effect of the psilocybin itself, expectancy bias is also noted. Escitalopram and psilocybin-assisted therapy are also usually delivered in quite different modalities; combining the two in this trial design may account for some of the different outcomes. As the trial group was characterized by mild-to-moderate depression, generalizability to more severe or to treatment-resistant populations is limited. Larger and longer trials are required to investigate the relative advantage of psilocybin over standard anti-depressant treatments. These trial results also raise the question of outcome measures, namely by what criteria we advance novel treatments and assess outcomes for depression. Studies to date have been driven by the measurements of negative symptomology and not overall well-being or positive affect.

Most recently, Davis et al. (2021) reported results from a randomized, waitlist–controlled clinical trial conducted with adults from 21 to 75 years old (mean age 39.2) with MDD. Excluded were individuals currently using antidepressant medications, and with histories of psychotic disorder, serious suicide attempt, or hospitalization. Participants (n = 27, 16 women) were randomized into immediate treatment (n = 15) or to the delayed treatment group (n = 12). Primary outcomes were measured for four weeks. Two doses of psilocybin were given, along with 11 hours of psychological support. The main outcome measurements of HAM-D were taken at baseline and weeks one and four (for immediate treatment group), and weeks five and eight (for delayed treatment group). Participants also completed the QIDS-SR as a secondary outcome. Among the 24 participants who completed the intervention and follow-up assessments, 17 (71%) had a clinically significant response at week four, and 13 (54%) participants met the criteria for remission of depression at that same time period.

The Davis et al. (2021) trial suggests that psilocybin-assisted therapy results in substantial, rapid, and enduring antidepressant effects among people with MDD. Of particular note is that while rapid antidepressant effects are similarly reported for ketamine, psilocybin demonstrated no addiction risk as can occur with ketamine, few adverse effects, and greater durability or persistence of therapeutic effect than has been demonstrated for ketamine. The authors report findings 2.5 times greater than the effect sizes found in psychotherapy alone and greater than four times the effect sizes found in contemporary psycho-pharmacological depression treatment studies.

A number of secondary publications rooted in the core clinical trials of psilocybin-assisted therapy have examined specific features or outcomes, often through qualitative examinations of patient experiences. Wide variation in experience among participants include revived emotional responsiveness and decreased rumination (Mertens et al., 2020; Roseman et al., 2018); increased emotional range (Belser et al., 2017); reduced response to negative affective stimuli and increased cognitive flexibility (Barrett, 2019; Doss et al., 2021); mysticomimetic as well as dysphoric experiences (Nielson et al., 2018; Swift et al., 2017); motivation for change (Nielson et al., 2018) and decreased avoidance (Watts et al., 2017); self-compassion and death acceptance (Malone et al., 2018; Swift et al., 2017); insights into self-identity (Bogenschutz et al., 2018; Noorani et al., 2018); relational embeddedness and increased sense of connectivity (Belser et al., 2017; Lyons & Carhart-Harris, 2018a; Watts et al., 2017); personality change with increased openness and extraversion (Erritzoe et al., 2018; MacLean et al., 2011); as well as decreased pessimism (Lyons & Carhart-Harris, 2018b) and decreased anhedonia (Stroud et al., 2018).

Although early investigations have indicated the antidepressant potential of psilocybin, the underlying mechanisms that explain its therapeutic action are not well understood (Anderson et al., 2021). Recently Daws et al. (2022) published an analysis of the fMRI data from the Carhart-Harris et al. (2016a) and Carhart-Harris et al. (2021) trials. Results from the Carhart-Harris et al. (2016a) open-label trial showed a significant decrease in brain network modularity one day after psilocybin, which corresponded with improvements in depression severity for six months. Cartography network analysis demonstrated a decrease in connectivity *within* the default-mode

network (DMN), yet an *increase* in DMN connectivity with higher-order networks including the executive network and salience network. Such global network integration, along with decreased DMN modularity, has been associated with lower depression scores. Similar fMRI results were reported at the endpoint of the Carhart-Harris et al. (2021) double-blind RCT comparing psilocybin to escitalopram: a significant decrease in brain modularity from baseline in the psilocybin group that corresponded with reductions in depression severity. Significantly, there were no changes in modularity in the escitalopram group, nor significant correlations between BDI scores and changes in modularity, indicating that the relationship between enhanced global integration, dynamic flexibility of brain networks, and improvements in depression severity are specific to psilocybin (Daws et al., 2022). Analysis of these studies provides more empirical evidence for the role of DMN modularity in depression severity and suggests the potential of the acute action of psychedelics in reducing network modularity and increasing global network integration. Daws et al. (2022) are careful to make clear that these results are specific to depressed populations, yet based on previous research they suggest that the global changes in functional network organization may be found with other psychedelics, namely LSD and ayahuasca (Luppi et al., 2021; Pasquini et al., 2020).

A recent review (Heuschkel & Kuypers, 2020) identified clear synergies between mindfulness meditation and psilocybin for the treatment of major depression, with similar effects noted on mood, social skills, and neuroplasticity. The enhanced affective self-regulation and improved stress response associated with mindfulness meditation practices are thought to potentiate, prolong, and synergize with the effects of psilocybin toward attenuation of cognitive associations, cognitive disinhibition, and global neural network disintegration for added therapeutic benefit.

These early Phase 1 and more current Phase 2 clinical trials do suggest that psilocybin, when administered with psychological support and in a supportive setting, has an antidepressant effect among individuals with major depressive disorder. Phase 3 trials are currently underway in the U.K. and U.S.

4.2.2 Suicide

In Canada, the prevalence of suicidal ideation among those aged 15 and over is measured to be 3.3%, suicidal planning 1.1%, and suicide attempt(s) 0.5% (Palay et al., 2019). Suicide and suicide attempts take an enormous emotional toll on the families and friends of those who die and on survivors of attempts (Florence et al., 2015). Additionally, there is a tremendous economic cost associated with suicide, with a single suicide estimated to cost approximately \$1.3 million USD (Florence et al., 2015). This is primarily due to lost income for families, lost productivity for employers, and medical costs for individuals and families. There are no known medication or strategies approved to alleviate acute suicidality in the emergency department. Further, there are limitations to existing treatments to decrease suicidal ideation or plans in those with moderate to severe depression.

Sexton et al. (2020) tested the associations between lifetime use of psychedelics (phenethylamines, tryptamines, lysergamides) with past-month psychological distress and past-

year suicidality among respondents to the 2008-2017 National Survey on Drug Use and Health (n = 260,964,827). They found that lifetime use of classic psychedelics (tryptamine and lysergamide) was associated with decreased odds of past-month psychological distress and past-year suicidal thinking. Novel phenethylamine use was associated with increased odds of past-year suicidal thinking and planning, with no other significant associations. In a similar study based on responses to the National Survey on Drug Use and Health 2008-2012 (n = 190,000), Hendricks et al. (2015b) also found significantly reduced odds of psychological distress and suicidal thinking were associated with lifetime classic psychedelic use. This national survey data is correlational and indicates the need for more rigorous study on the association between psychological well-being, psychological distress, and suicidal thinking with lifetime psychedelic use, with attention to different classes of psychedelics and modes of consumption.

Ketamine

Ketamine can be a rapid antidepressant/anti-suicidal intervention in a range of settings including among hospitalized patients, those presenting in emergency departments, as well as in outpatient settings (Bahji et al., 2021; Hochschild et al., 2021; Wilkinson et al., 2018). In a systematic review (10 studies) and individual participant data meta-analysis (n = 167), Wilkinson et al. (2018) reported that one dose of ketamine quickly relieved suicidal ideation as measured by clinician and self-reported measures. Reductions in suicide ideation were reached as early as 24 hours; 89.2% of those receiving ketamine vs 42.9% of controls remained free of suicidal ideation one-week post-treatment (Wilkinson et al., 2018). Another meta-analysis conducted by Xiong et al. (2021) analyzed nine RCTs (n = 197) with results suggesting that a single dose of IV ketamine or intranasal esketamine was associated with significant decreases in suicidal thoughts 2hr, 4hr, and 24hr following medication administration. A 2021 systematic review of all RCTs investigating the effect of ketamine on suicidal ideation found four of five RCTs examined IV racemic ketamine (0.5mg/kg) and found advantage for ketamine over control for rapid reduction of SI in patients with acute depression (Hochschild et al., 2021). Two studies examined intranasal esketamine in depressed suicidal patients, finding no advantage for ketamine over saline; one study of six-week outcomes after a single IV dose of ketamine found sustained benefit in reducing SI relative to 24-hour post dose (Hochschild et al., 2021).

Bahji et al. (2021) also highlight the role of ketamine and esketamine as effective and rapid-acting medications to reduce suicide risk for those in acute crisis. Wilkinson et al. (2018) indicate that ketamine has a good safety profile with moderate evidence that it is effective in reducing acute suicidality for up to two weeks. Bahji et al. (2021) found that suicidality scores decreased significantly with ketamine treatment but reductions in suicidality were not significant at the two-and four-week timepoints, indicating that effects on suicidality could wane over time. In a meta-analysis of five clinical trials where a single dose of IV ketamine was given to 99 people with acute suicidal ideation and changes in suicidal ideation were measured within four hours of treatment, it was shown that ketamine caused a large and consistent decrease in suicidal ideation (with similar effects of IV bolus vs infusion; Bartoli et al., 2017). The same authors concluded that across studies the effect of ketamine on suicidal ideation varied over time, which could have been the result of the low number of studies and power issues at the different time points (Bartoli et al., 2017).

Maguire et al. (2021) carried out a systematic review of three studies (N = 61) of ketamine (0.2mg/kg) use for acute suicidal ideation in the emergency department and concluded that none of the studies provided convincing data for the efficacy of ketamine in this setting for prolonged relief of acute suicidality. In this review, co-occurring conditions included depressive disorder, bipolar depressive disorder, and dysthymia. However, all three studies excluded those with substance use disorders and positive urine drug screen, and two studies excluded those with other psychotic disorders. The studies assessed suicidality with the Beck Scale for Suicidal Ideation (BSS) or the Scale for Suicidal Ideation (SSI) as well as depressive symptoms at baseline and then multiple time points after ketamine administration (maximum 2 weeks post ketamine treatment). A meta-analysis couldn't be completed as individual data were not available. The review showed no adverse effects and the authors concluded that ketamine shows weak evidence for transient "hastening of symptomatic relief" but that it cannot be routinely recommended for acute suicide ideation in the emergency department compared to "simple passage of time" (Maguire et al., 2021). The authors also highlighted that approximately one-fifth of visits for self-harm or suicide ideation were identified as having a substance use disorder and that half of those with self-harm revealed alcohol use prior to admission. Future studies should ensure sufficient attention to this co-morbidity in study design and inclusion/exclusion criteria.

4.2.3 Depressive Phase of Bipolar Disorder

Bipolar disorder, formerly known as manic-depressive disorder, is characterized by severe mood swings that may impair normal functioning at school, work, and in relationships (Müller-Oerlinghausen et al., 2002). Bipolar disorder (BPD) is classified into three types: Bipolar I disorder, Bipolar II disorder, and Cyclothymic disorder. BPD I is characterized by manic episodes that last at least seven days, often with episodes of depression that may last two weeks. BPD II is characterized by depressive and hypomanic episodes, instead of full mania. Cyclothymia is defined by longer episodes (approx. 2 years) of hypomania and depression that may not meet diagnostic requirements for either. It has been estimated that approximately 1.5% of the Canadian adult population suffers from bipolar disorder (Palay et al., 2019). In its most severe form, bipolar disorder is often accompanied by mania or depression and profound psychosis (Müller-Oerlinghausen et al., 2002). The mortality rate for individuals with bipolar disorder is significantly higher than that of the general population, with an estimated 33% of affected individuals attempting to take their own life and 10-20% successfully doing so (Müller-Oerlinghausen et al., 2002). Pharmacological options for the treatment of bipolar disorder include lithium salts, carbamazepine, and valproate (Müller-Oerlinghausen et al., 2002). While lithium salts are considered effective in treating the acute or dysphoric mania associated with bipolar disorder, experts note that the treatment of bipolar depression remains 'unsatisfactory' (Baldessarini et al., 2018). Inadequate medication adherence due to adverse effects and prohibitive costs further limits efficacy of available pharmacotherapies (Baldessarini et al., 2018). Due to the high risk of suicide among individuals with bipolar disorder, there is a desperate need for alternative treatment approaches. Nevertheless, a BPD diagnosis is anecdotally considered contraindicated for psychedelic use and many clinical trials use this as an exclusion criterium. Also significant, many ayahuasca ceremony facilitators consider people

diagnosed with BPD to not be good candidates for use and often discourage or exclude their participation. We are only aware of one researcher, psychiatry doctoral candidate Benjamin Mudge, who is actively investigating the use of ayahuasca among people with BPD. In Mudge's doctoral research, he has analyzed qualitative interviews from 75 participants with BPD who have drunk ayahuasca and is developing an ayahuasca protocol specifically for bipolar brains (see: <https://bipolardisorder.me/research-projects/>).

Ketamine

Ketamine has been studied for treatment resistant bipolar disorder, with one meta-analysis finding that patients given ketamine had a significant response at one-day post-infusion (Fornaro et al., 2020). Another review of eight studies determined that ketamine (0.5mg/kg IV over 40 minutes) given weekly could be useful in the treatment of bipolar depression with prominent anhedonia (Gałuszko-Węgielnik et al., 2019). As well, a meta-analysis of 20 peer reviewed RCTs studying unipolar and bipolar depression found that at 24 hours, ketamine showed the largest effect of reducing depressive symptoms compared to controls and that a significant difference was shown for up to seven days after a single dose (Kryst et al., 2020). Bahji et al. (2021) report that while several studies support a role for IV ketamine as a treatment for bipolar depression there was no significant difference in clinical response between people with unipolar major depression compared to those with bipolar depression. Grabski et al. (2020) in their systematic review of 17 studies (four included unipolar and bipolar depression) also found inconclusive results.

Diazgranados et al. (2010) conducted a six-week, placebo-controlled cross-over trial that investigated the use of ketamine for treatment-resistant acute bipolar depression. This study was replicated by Zarate Jr et al. (2012) for participants with BPD I and II. Both studies maintained individuals on therapeutic levels of lithium or valproate and administered IV infusion of either ketamine hydrochloride (0.5 mg/kg) or placebo on two test days two weeks apart. Neither study included a psychotherapeutic intervention as part of the ketamine therapy. Diazgranados et al. (2010) and Zarate Jr et al. (2012) both found that depressive symptoms significantly improved within 40 minutes (as measured by the MADRS) in individuals who received ketamine compared to placebo. Additionally, the effect remained significant through day three post-infusion, thus providing initial evidence for the rapid antidepressant effects of ketamine on treatment-resistant BPD and BPD I and II without psychotic features (Fornaro et al., 2020).

4.2.4 Psychedelics for Depression: Summary

Ketamine, ayahuasca, and psilocybin have all been recently trialed among human subjects with disorders of depression. Older trials using LSD or psilocybin in treatment of neurosis or mood disorders in the early era of research (1940-1974) are characterized by poor research design and limited generalizability, though evidence was accumulated on how to design the next generation of clinical trials. No contemporary single-drug clinical trials for the treatment of depression were found for LSD, DMT, 5-MeO-DMT or mescaline (including peyote/huachuma),

though some are being planned or currently underway. Trials that have assessed the safety and efficacy of LSD among healthy subjects (Dolder et al., 2016; Schmid et al., 2015) and subjects with anxiety associated with life-threatening diseases (Gasser et al., 2014) have also reported its positive effects on mood yet offer no conclusions specific to LSD and the treatment of depression.

Intravenous, intranasal, and to a lesser extent, oral ketamine have been demonstrated to have rapid but transient anti-depressant effects. Repeated dosing is indicated for sustained effect, and intravenous administration appears preferable. The majority of ketamine trials in the treatment of depression use single doses, though more recent studies report that repeated infusions of ketamine may help prolong the therapeutic effects. Although various Phase 3 clinical trials are currently examining the therapeutic effects of ketamine for mental disorders, the more expensive esketamine has already been granted FDA and Health Canada regulatory approval for treatment of depression, and ketamine clinics for the treatment of depression and PTSD are active in Canada and the USA. Overall, the science on the efficacy of ketamine for depression remains inconclusive and research into ketamine for depression is significantly greater than the number of trials investigating other psychedelic compounds in the treatment of depression. This is due in no small part to the fact that ketamine is an already-approved medication that is readily applied for clinical and research use, while other psychedelics remain much more tightly controlled and difficult to obtain for research purposes.

Ayahuasca has been examined as a treatment for depression in three small trials, with an aggregate study population of only 50 people. Nevertheless, these early Phase 1 trials not only establish safety and tolerability for some patients, but also indications of efficacy in the form of rapid-onset anti-depressant effects sustained for three weeks (Osório et al., 2015; Sanches et al., 2016; Palhano-Fontes et al., 2018). Larger, more rigorous placebo-controlled trials are indicated, as well as longer follow-up data. As discussed in Section 7.1, ayahuasca is a culturally significant plant in many South America societies and therefore researchers must be attentive to political and sociocultural factors as well as issues of sustainability.

Psilocybin has been investigated as a trial drug in the treatment of depression in four distinct phase 2 trials involving 115 participants and is currently in Phase 3 investigations in both the U.K and U.S. Psilocybin has been demonstrated as safe, tolerable, and effective in the reduction of depressive symptomology for up to 24 weeks with sustained effects measured to six months. Mixed results of a recent head-to-head trial between psilocybin and escitalopram raise the question of choice of outcomes measured, but demonstrate the value of an open science philosophy by publishing negative or mixed results. The proven safety profile as well as anti-depressive and anxiolytic effects of psilocybin are further being investigated for relief of end-of-life distress.

A recent meta-analysis of RCTs examining the efficacy of serotonergic psychedelics for mood and depressive symptoms also provides a good summary of the state of knowledge in this area (Galvão-Coelho et al., 2021). The meta-analysis included 12 eligible studies – eight focused on psilocybin, three on LSD, and one on ayahuasca. In a pooled analysis across psychedelics and for patients with a mood disorder, significant effect sizes were observed on the acute, medium

(two to seven days after treatment) and longer-term outcomes favoring psychedelics on the reduction of depressive symptoms. Secondary analysis by psychedelic substance revealed moderate effect sizes for both psilocybin and LSD with a slightly larger effect size for LSD. An analysis of the longer-term data (16-60 days after treatment) indicated that psilocybin maintains its response on negative mood reduction, with a moderate effect size compared to placebo. It should be noted that this meta-analysis investigates classic serotonergic psychedelics for mood disorder patients and healthy volunteers, and only two out of 12 studies included participants with a diagnosis of depression. Therefore, the meta-analysis is not meant to draw conclusions about the clinical use of classic psychedelics for depressive disorders (MDD, BDP, etc.). Nevertheless, Galvão-Coelho et al. (2021) provide an excellent synthesis across well-designed studies and also provide a succinct summary of the challenges to be overcome in measurement and research design, including the importance of considering the psychotherapeutic component of psychedelic-assisted interventions and the need to tease out its relative contribution with proper study design and statistical assessment of independent or moderating impact.

In summary, certain psychedelics present a promising route of rapid relief and potentially long-term remission for depressive disorders for some individuals. Given the preponderance of research into ketamine for depression and overall inconclusive results, a Canadian research agenda may want to more heavily weight investments into other compounds and forms of therapy, namely psychotherapies complemented by psilocybin or potentially LSD or ayahuasca. Another consideration for future ketamine studies is to investigate ketamine-assisted psychotherapy (KAP) instead of ketamine on its own. Although use of such psychedelics for depression are considered to be a novel yet safe, viable, and potentially efficacious form of treatment, there is need for continued study and support. Early results are promising, especially for conditions with high rates of treatment resistance. Importantly, the established therapeutic benefits of the study drugs always occur within a larger therapeutic framework, generally in the form of psychotherapeutic support before, during, and after dosing sessions. Considering the widespread grey market in online and in-person sales of Psilocybe mushroom preparations containing psilocybin in Canada, there is further impetus for a continued program of clinical trials examining the therapeutic applications and any known possible clinical benefit from psilocybin and other psychedelic-assisted therapies.

4.3 Outcomes Related to Anxiety Disorders Including PTSD

4.3.1 Generalized Anxiety Disorder (GAD) and Social Anxiety Disorder (SAD)

General anxiety disorder (GAD) and social anxiety disorder (SAD) are two of the most common mental health challenges amongst Canadians (Stein & Sareen, 2015). In 2012, an estimated 2.4 million Canadians aged 15 years and older reported lifetime symptoms of GAD (Pelletier et al., 2017). Additionally, about 12% of individuals with GAD also meet criteria for SAD (Kessler et al., 2005).

Individuals with GAD have excessive worry and anxiety about everyday events without obvious reason (Locke et al., 2015). This is often accompanied by fear and avoidance of the judgements of others, primarily due to concerns that they may say or do something to elicit embarrassment (Stein & Stein, 2008). The neurobiology and genetic basis of GAD is poorly understood and often comorbid with other mood disorders such as MDD, bipolar disorder, and other chronic illnesses resulting in extensive disability and excessive use of medical services (Hidalgo & Sheehan, 2012). SAD is also considered a risk factor for problematic substance use (Stein & Stein, 2008).

Traditional treatments for GAD and SAD include psychotherapy and medications such as antidepressants, buspirone, or benzodiazepines (Locke et al., 2015). While these conventional pharmacological treatments are considered effective, they can take weeks to achieve their full effects, often have adverse side-effects, and many patients do not achieve symptom relief from them (Locke et al., 2015). Thus, many Canadians could benefit from alternative therapeutic models for anxiety and anxiety-related disorders, particularly therapies that do not require daily dosing for up to 12 months.

Ketamine

A scoping review conducted by Banov et al. (2019) analyzed case reports and multiple small but well-controlled studies investigating the efficacy and safety of ketamine for the management of anxiety and anxiety spectrum disorders. Results of their analysis provide sufficient evidence to suggest ketamine may be an effective and safe novel strategy for managing treatment-resistant anxiety patients. Another review (Dore et al., 2019) analyzed outcome data from 235 patients who received Ketamine-Assisted Psychotherapy (KAP) from three distinct practices using similar methods. They conclude that KAP is an effective method for decreasing anxiety and depression symptoms in a private practice setting, particularly for older patients and those with severe symptoms.

Glue et al. (2017) delivered ascending doses of subcutaneous (SC) ketamine (0.25, 0.5, 1.0 mg/kg) at weekly intervals to a group of 12 patients. All 12 patients had a diagnosis of SAD and 10 also had a diagnosis of treatment-resistant GAD. Ten of 12 patients responded to treatment at 0.5-1.0 mg/kg dosages, reporting reduced anxiety within one hour of drug administration. Eight of 12 patients experienced more than a 50% reduction in HAM-A and/or Fear Questionnaire (FQ) scale scores at 2-hours post-infusion of a 0.5-1.0 mg/kg dose (Glue et al., 2017). The same group conducted another trial of 20 patients who responded to acute open-label ascending doses of ketamine (0.25, 0.5, 1 mg/kg; Glue et al., 2018). 15 patients had GAD and 18 had SAD. Patients were given one or two weekly ketamine doses of 1 mg/kg SC ketamine. FQ and HAM-A ratings decreased by approximately 50%. Clinician-Administered Dissociative States Scale (CADSS) mean scores decreased from 20 points to 8.8 points from weeks 1 to 14, respectively.

The same research group completed another clinical trial aiming to replicate prior findings using a more robust study design (Glue et al., 2019). In this double-blind, psychoactive-controlled study the authors administered ascending doses of ketamine (0.25, 0.5, 1 mg/kg) to 12 patients

at weekly intervals, with a very low dose (0.01 mg/kg) inserted randomly into the ketamine sequence. Participants experienced improvements in anxiety ratings within an hour of receiving ketamine, and these improvements were sustained for up to one week. The most recent clinical trial from this group investigated the efficacy of an extended-release oral ketamine tablet in seven patients with treatment-resistant depression and/or anxiety (Glue et al., 2020). Depression and anxiety ratings improved over 96 hours with all patients experiencing >50% improvements in mood ratings.

A double-blind, randomized, placebo-controlled crossover trial conducted by Taylor et al. (2018) compared IV ketamine to placebo among 18 adults with a DSM-5 diagnosis of SAD. Participants were administered ketamine (0.5 mg/kg over 40 minutes) and placebo infusions in random order with a 28-day washout period between infusions. They observed a significant reduction in anxiety (>35%) relative to placebo as measured by the Leibowitz Social Anxiety Scale (LSAS), but not the VAS-Anxiety measure (which requires 50% reduction of symptoms to be considered significant). Participants were significantly more likely to exhibit a treatment response within two weeks post-ketamine infusion compared to placebo as measured by both the LSAS and the VAS. The authors concluded that their study provides initial evidence for the efficacy of IV ketamine in reducing anxiety. In a study of the effects of ketamine on participant EEG, Shadli et al. (2018) conducted a double-blind trial with three ascending ketamine dosages (0.25, 0.5, and 1 mg/kg) and using midazolam (0.01 mg/kg) as an active control. 12 participants with refractory GAD (n = 10) and/or SAD (n = 12) and no comorbid depression (i.e., excluded MADRS >20) were given SC ketamine in ascending order at one-week intervals, with midazolam inserted into the schedule at random. Participants continued their normal medication and/or psychotherapy regimens for the duration of the trial. EEG was monitored predose and two hours post-dose, and anxiety was assessed using the FQ and HAM-A. Eight of 12 patients (67%) reported a significant reduction (>50%) in HAM-A and/or FQ scores after the 0.5 or 1.0 mg/kg dose. Their results demonstrated that ketamine significantly decreased FQ scores in a dose-dependent fashion up to 1mg/kg, after which benefits either plateaued or reduced (Shadli et al., 2018).

4.3.2 Anxiety in Bipolar Disorder and Unipolar Depression

Ketamine

As mentioned in section 4.2.3, Diazgranados et al. (2010) conducted a randomized, double-blind, placebo-controlled, crossover add-on study among treatment-resistant DSM-IV bipolar depression (n = 18). Participants were maintained on therapeutic levels of lithium or valproate and received either IV ketamine (0.5mg/kg) or saline placebo on two test days two weeks apart. Depressive symptoms were significantly reduced according to MADRS scores within 40 minutes, with the largest effect size at day two, and response to ketamine lasting an average of 6.8 days. While this trial had a small participant population with several dropouts, the authors concluded that results provided evidence for the rapid antidepressant effects of ketamine among people with BPD. Significant and rapid improvements in anxiety were also observed as measured by the HAM-A and VAS, lasting through day two (Diazgranados et al., 2010).

Zarate Jr et al. (2012) sought to replicate these results in a double-blind, placebo-controlled study investigating the effects of ketamine in 15 patients diagnosed with DSM-IV BPD I or II without psychotic features. As in the previous trial, patients were maintained on a therapeutic dose of lithium or valproate and received a single IV dose of 0.5 mg/kg ketamine. No structured psychotherapy was provided. In addition to the significant rapid antidepressant and antisuicidal effects, scores on the HAM-A and VAS-Anxiety also improved significantly within 40 minutes of infusion.

In post-hoc analysis of these two studies, Ionescu et al. (2015) delineated the patients between anxious (n = 21) and non-anxious (n = 15) bipolar depression. Results suggested that ketamine had rapid and short-term antidepressant effects for participants with both anxious and non-anxious BPD, exhibiting no group difference in HAM-A or CADSS scores. This study has implications for the treatment of depressive symptoms among people experiencing anxious bipolar disorder, which may represent a more severe subtype compared to non-anxious bipolar and is typically more difficult to treat with traditional therapies (Ionescu et al., 2015). While this is encouraging for the reduction of depressive symptoms for people with anxious bipolar depression, the results do not indicate that ketamine reduced anxiety among the participants.

4.3.3 Anxious Symptoms in Depressed Patients

Major depressive disorder (MDD) is commonly presented with comorbid anxiety disorder (Goldberg & Fawcett, 2012), and is associated with poor treatment outcomes (Gaspersz et al., 2018). It is estimated that 42-78% of all depressed patients suffer from comorbid anxiety (Gaspersz et al., 2018). Individuals with major depression and 'anxious depression', as compared to individuals solely affected by major depression, may have worse severity of depressive symptoms (Fava et al., 2006; Goldberg & Fawcett, 2012; Lamers et al., 2011), increased risk of suicide (Fawcett, 2013; McIntyre et al., 2016; Seo et al., 2011), and poorer treatment response (Davidson et al., 2002; Fava et al., 2008).

Ketamine

In a case series published by Irwin and Igiewicz (2010), two patients with depressive disorder were given one oral dose of ketamine (0.5 mg/kg). Symptoms of both depression and anxiety were improved within one hour, and the effect was sustained for up to one week.

Ballard et al. (2014) analyzed data from four clinical trials studying the effectiveness of ketamine with treatment-resistant depression. 133 subjects diagnosed with either major depression (n = 98), or type I (n = 19) or II (n = 16) bipolar depression were given 0.5 mg/kg IV ketamine over 40 minutes. In addition to improvements in depressive symptoms and suicide ideation, anxiety symptoms as measured by the HAM-A also improved.

4.3.4 Post-Traumatic Stress Disorder

PTSD occurs in individuals who have experienced or witnessed a traumatic event such as war, sexual violence, a natural disaster, a serious accident, a death threat, or serious injury (American Psychiatric Association, 2017). Increasingly, PTSD is also thought to result from multiple cumulative exposures to traumatic situations, as for example unstable domestic life or in the work of emergency response teams, police officers, or correctional officers. Symptoms of PTSD include intrusive thoughts, avoiding reminders of the traumatic event, alterations in cognition and mood, and alterations in arousal and reactivity (American Psychiatric Association, 2017).

Lifetime PTSD prevalence in Canada is estimated to be approximately 9.2% (Van Ameringen et al., 2008). PTSD is a serious mental health condition and public health problem with a high burden of illness as well as enormous and growing social and economic implications (Mitchell et al., 2021). PTSD is thought to affect 4-5% of the population worldwide and up to 17% of military veterans (Dursa et al., 2014; Hoge et al., 2004; Kessler et al., 2004). PTSD is a strong predictor of disability in community and veteran populations (Mitchell et al., 2021). People with PTSD have a higher risk of suicide and may have multiple co-morbidities including cardiovascular disease, chronic pain, dissociation, depression, substance use disorder and childhood trauma (Mitchell et al., 2021; Conner et al., 2014; Edmondson & Cohen, 2013). Available treatments include psychotherapy and SSRI medications, though both are limited in efficacy. PTSD has a high rate of relapse (Goetter et al., 2015; Lee et al., 2016) and 40-60% of patients do not respond to current pharmacotherapies (Mitchell et al., 2021).

MDMA-Assisted Therapy

A pooled analysis of six phase 2 RCTs for MDMA-assisted psychotherapy suggest safety and efficacy (Mithoefer et al., 2019). Each trial included three 90-minute psychotherapy sessions before the first MDMA exposure, and each MDMA session was followed by three to four psychotherapy sessions. Pooled results of all trials found a large treatment effect and significant reductions in depression (BDI-II) and PTSD (CAPS-IV) scores. MDMA-assisted psychotherapy was well tolerated in a large sample and results of these phase 2 trials led to the FDA granting Breakthrough Therapy designation as well as support for phase 3 clinical trials.

One limitation to MDMA-assisted therapy (MDMA-AT) clinical trials is the variation in study design and methods. Thus, Wang et al. (2021) conducted two multisite open-label trials of MDMA-AT for PTSD to assess the feasibility of scaling this manualized therapy across 14 clinical trial sites in North America (12 USA, 2 Canada). Cotherapist dyads were trained under clinical supervision and the investigators measured treatment fidelity to the MAPS therapy manual for MDMA-AT with adherence ratings conducted by independent raters. Participants (n = 37, 22 women, average age 35.6) were paired with 37 distinct therapist dyads. MDMA-AT was provided over 9 to 15 weeks, with three preparation sessions, three dosing sessions, and three integration sessions. Adherence rating scores were high across all co-therapist dyads and sites and MDMA was well-tolerated among patients. CAPS-5 scores decreased following three MDMA-AT sessions at 18 weeks after baseline. At the primary endpoint 91.9% (n = 34) of all

participants had a clinically meaningful reduction in their CAPS-5 scores and 75.7% (n = 28) no longer met PTSD criteria.

The most common adverse experiences included headache (68%), muscle tightness (49%), insomnia (35%), anxiety (32%), nausea (30%), fatigue (27%), and suicidal ideation (27%). The most frequent in-session adverse experiences were muscle tightness (73%), headache (62%), insomnia (49%), nystagmus (30%), and nausea (27%). Most participants rated adverse experiences as mild-to-moderate. Five severe adverse experiences (syncope, headache, anal fissure, exacerbation of suicidal ideation, and suicide attempt) occurred between 5 and 78 days post-experimental session.

While adherence ratings were useful for measuring consistency across sites and within MDMA-AT, the authors recognized the possibility of leniency bias (i.e., raters may have desired MDMA-AT to be positively evaluated) and/or confirmation bias among the raters. Further, only a subset of integration sessions were used for adherence ratings. These multisite studies demonstrate that recently trained therapist dyads can achieve safety and efficacy in reducing severity of PTSD symptoms, and that MDMA-AT is a scalable treatment which can be effectively delivered by trained therapists across varied locations (Wang et al., 2021).

Mitchell et al. (2021) reported a Phase 3 double-blind, placebo-controlled, multisite RCT that investigated MDMA-AT for severe PTSD, including comorbidities. Patients with PTSD (n = 90) were enrolled and randomized to receive manualized therapy with MDMA or with placebo, combined with three preparatory and nine integrative therapy sessions. PTSD symptoms (primary outcome) were measured at baseline and two months after the last session with the Clinician-Administered PTSD scale (CAPS-5) in the DSM-5. Functional impairment (secondary outcome) was measured with the Sheehan Disability Scale (SDS) at the same time points. MDMA was found to induce significant and robust attenuation in CAPS-5 scores when compared to placebo and to significantly decrease the SDS total score from baseline to 18 weeks after baseline. Treatment efficacy was equal for participants with comorbidities that are associated with treatment resistance (e.g., depression, childhood trauma, suicidality, alcohol and substance use disorders, and dissociation). MDMA did not result in adverse events including non-medical use, suicidality, or increased heart contraction times (i.e., QT prolongation). Study results indicate that compared with manualized therapy with inactive placebo, MDMA-AT is demonstrably safe and efficacious in some individuals with severe PTSD. Indeed, trial data suggest that MDMA has an equivalent or superior safety profile compared to first-line SSRIs for the treatment of PTSD.

Treatment-emergent adverse events were more prevalent in the MDMA study arm and were typically transient and mild-to-moderate in severity. Adverse experiences included muscle tightness, decreased appetite, nausea, hyperhidrosis, and feeling cold. No increase in adverse events related to suicidality was observed in the MDMA group. A transient increase in systolic and diastolic blood pressure as well as heart rate were observed in the MDMA group. Reports of severe adverse experiences were limited to the placebo group. MDMA did not increase the occurrence of suicidality, potential for recurrent or non-medical use, or cardiovascular risk in this trial. Study limitations noted include small sample size, the relative homogeneity of the study

cohort, the lack of long-term follow-up data, difficulties in blinding the effects of MDMA, and the fact that safety data was collected by the study therapists. Despite these limitations, the investigators concluded that MDMA-AT is a potential breakthrough treatment meriting expedited clinical evaluation – the findings also suggest the importance of advancing compassionate access policies and programs in advance of standard regulatory approval.

Tedesco et al. (2021) conducted a systematic review and meta-analysis on the efficacy of MDMA-assisted psychotherapy for treatment-resistant PTSD. Ten studies (yielding 16 articles) conducted between 2004 and 2020 in five different countries were included, with a total sample size of 168 patients, all of who met the DSM-V criteria for PTSD. Studies were primarily in outpatient settings and all were funded by MAPS (USA) and therefore utilized the same manualized supportive therapy model developed and owned by MAPS. Five trials were in response to chronic PTSD lasting from 7-29 years, and the other five trials had a shorter criterion of persistent PTSD symptoms lasting longer than six months. Results from the meta-analysis found promising evidence for the therapeutic potential of MDMA-assisted psychotherapy in the treatment of PTSD. Further, Tedesco et al. (2021) suggest that the pharmacological profile of MDMA may provide the basis for novel drug developments to treat patients with a range of treatment-resistant mental disorders.

These trials were characterized by sizable differences in methodology across sites, limiting the ability to generalize findings. Doses often differed, as did dosing regimens, and studies required different wash-out periods from SSRIs. While half the studies did not report at all on prior therapy, other studies reported mean previous therapy of 58.5 to 85.8 months. The number of MDMA sessions ranged from one to three per study, and the number of follow-up sessions also varied between studies. Short term follow-up ranged between one week and five months, while longer-term follow-up ranged between six and 74 months.

Aggregated data from the 10 studies demonstrated that subjects who underwent MDMA-assisted therapy were more likely to show clinically significant responses in comparison to controls who received psychotherapy without MDMA. The pooled sample of ten studies provides a more statistically significant assessment which favors MDMA use than is possible for each study alone. Out of a total of 130 participants in the experimental group, 100 participants responded positively, while 10 of the 38 participants in the control group responded positively. Remission rates varied from 56% to 100% in the experimental groups while 10 of 38 individuals in the control group demonstrated some remission of symptoms.

Effects of two or three MDMA-AT sessions were found to last for months, demonstrating persisting effects of treatment. All 10 studies demonstrated a baseline severity CAPS-5 score reduction of at least 30%, with a noted positive effect for higher doses of MDMA (75-125mg). Qualitative reports of improvements in quality of life, improvements in mood and global function, relationship domains and substance use were documented in some trials, but such data were not systematically collected. Analyses of adverse experiences reported suggest that MDMA is well-tolerated between the range of 40 mg to 187.5 mg. The risk profile includes side effects of anxiety, diminished appetite, headache, and jaw tightness, but each are transient and typically

self-resolve. The results of this meta-analysis support the use of MDMA as an adjunct treatment to psychotherapy for chronic, treatment-resistant PTSD.

A previous systematic review (Bahji et al., 2020) analyzing five MDMA-AT clinical trials with 106 participants (70% female, average age 35-40 years) demonstrated a high rate of clinical response and remission, a large effect size at reducing the symptoms of PTSD, and good safety and tolerability. The authors also noted preliminary evidence for other potential drug-assisted therapies, including psilocybin, ayahuasca, LSD and D-cylcoserine.

Overall, MDMA-AT clinical trials are limited by a number of factors, including small sample sizes, between-study variability, heterogeneity of experimental groups and difficulties in blinding, with quality of evidence from each study rated as moderate-to-high when assessed with the Cochrane Risk of Bias Tool (Bahji et al., 2020; Tedesco et al., 2021). Importantly, rates of co-morbidity were high: in Tedesco et al.'s (2021) review, five studies reported that 78.2% of participants had comorbid depression, while 38.2% had comorbid anxiety. Study findings may not be generalizable to all individuals with PTSD, given the focus on treatment-resistant PTSD.

Complex PTSD may benefit from more intensive psychedelic therapy and the use of MDMA as a precursor to serotonergic psychedelics. C-PTSD describes the multifaceted symptoms of traumatized patients who have endured prolonged abuse or neglect, reflecting a repeated trauma over time rather than a singular traumatic event (Herman, 1992). A recent Swiss study on a group therapy model using both MDMA and LSD found that MDMA enhanced motivation to change and strengthened therapeutic alliance when used in a group therapy model, while subsequent LSD sessions intensified and deepened the therapeutic process (Oehen & Gasser, 2022).

MDMA-assisted psychotherapy is the most advanced of any research based on clinical trials with psychedelics, and Phase 3 clinical trial results suggest regulatory approval within the near future. It is significant to note that what is being advanced is not simply MDMA for PTSD, but rather a manualized form of MDMA-assisted therapy, the protocols for which have been developed by MAPS-USA and are available online in the public domain for the general public to review and utilize.

Ketamine

A double-blind RCT conducted in 2014 provided the first robust evidence suggesting that ketamine may be an effective alternative pharmacotherapy for PTSD (Feder et al., 2014). 41 participants with chronic PTSD were randomized into treatment with IV ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg; active placebo) using a crossover design. Impact of Event Scale-Revised (IES-R) scores significantly improved in the ketamine treatment group compared to midazolam 24 hours post-infusion. Ketamine was additionally associated with a decrease in comorbid symptoms and improvement in overall clinical presentation (Feder et al., 2014).

In another study, a retrospective chart review of members of the armed forces (n = 147) who underwent at least one surgical operation at a burn center showed that the group receiving

intraoperative ketamine had significantly lower prevalence of PTSD (32 of 119) than the group that had not (13 of 28) (McGhee et al., 2008).

A 20-patient study found the duration of sustained response to Trauma Interventions Using Mindfulness Based Extinction and Reconsolidation (TIMBER) was increased when combined with ketamine therapy (Pradhan et al., 2018). A significant difference in the duration of PTSD symptom reduction was observed between the group that received TIMBER with ketamine (TIMBER-K) and the group that received TIMBER with placebo (TIMBER-P).

In the first RCT to test efficacy and safety of repeated IV ketamine infusions, 30 individuals with chronic PTSD were randomly assigned to receive six infusions of ketamine (0.5 mg/kg) or midazolam (0.045 mg/kg) over two weeks (Feder et al., 2021). At week two, mean Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) total score was significantly lower in the ketamine group than the midazolam group and 67% of the ketamine group were treatment responders, as compared to 20% in the midazolam group (Feder et al., 2021). Median time to loss-of-response was 27.5 days following a two-week course of infusions in the ketamine group.

Shiroma et al. (2020) conducted a small, open-label, proof-of-concept study in which 10 individuals received IV ketamine (0.5 mg/kg) 24 hours prior to their weekly prolonged exposure (PE) therapy (the gold standard for trauma therapy) for the first three weeks, followed by up to seven additional PE sessions. Over four months, CAPS-5 scores significantly decreased from baseline to end of treatment. These results suggested that repeated IV ketamine administration can be used with standard PE therapy to treat PTSD (Shiroma et al., 2020).

In another clinical trial, 15 individuals with chronic PTSD and major depressive disorder received six IV ketamine infusions (0.5 mg/kg) three times per week over a 12-day period (Albott et al., 2018). The remission rate for PTSD and major depressive disorder was 80% and 60%, respectively.

In an observational study, 30 US military veterans with combat-related PTSD received a series of six one-hour ketamine infusions administered with the goal of obtaining a transpersonal dissociative experience (Ross et al., 2019). Self-reported symptoms of PTSD as measured by change in score on the PTSD Checklist for DSM-5 decreased significantly from an average of 56.2 to 31.3 ($p < 0.001$), suggesting that high-dose ketamine infusion therapy may be valuable in treating combat-related PTSD.

5-MeO-DMT + Ibogaine for PTSD

A single publication (Davis et al., 2020a) has investigated 5-MeO-DMT in combination with ibogaine in the treatment of PTSD. Between 2017 and 2019, 65 US Special Operations Forces (SOF) veterans with trauma-related psychological and cognitive impairment completed a three-day psychedelic clinical program in Mexico. In 2019, Davis et al. (2020a) conducted a retrospective survey that examined mental well-being 30 days before and after participation in the combined 5-MeO-DMT and ibogaine clinical program. Of the 65 SOF veterans who completed the program, 51 (78%) completed the survey (mean age = 40, male = 96%, White = 92%). Survey data revealed significant and very large reductions in retrospective reports of

suicidal ideation, cognitive impairment, and symptoms of PTSD and anxiety, with a significant and large increase in the retrospective report of psychological flexibility. Additionally, participants rated the psychedelic experiences as one of the top five personally meaningful (84%), spiritually significant (88%), and psychologically insightful (86%) experiences of their lives.

Findings are limited by the retrospective self-report study design; therefore these results can be considered preliminary indications requiring further study. Results suggest this modality may offer a novel, rapid-acting, robust, and potentially cost-effective treatment for PTSD due to its ability to improve cognitive flexibility (Davis et al., 2020a). Further, the authors suggest that this study supports double-blind, placebo-controlled RCTs of ibogaine and 5-MeO-DMT as a transdiagnostic treatment approach for the veteran population.

4.3.5 Obsessive-Compulsive Disorder (OCD)

The prevalence of diagnosed OCD in Canada is reported to be 0.9% (Osland et al., 2018). In a population-based health survey (n = 25,097), individuals with OCD often experienced co-occurring mental disorders such as depression, bipolar disorder, GAD, and substance use disorder (Osland et al., 2018). OCD is marked by intrusive thoughts or obsessions that increase anxiety, as well as repetitive actions (compulsions) that consequently decrease anxiety (Stein, 2002). Some common obsessions and their compulsions include: (1) contamination concerns with washing compulsions; (2) precision obsessions with counting/ordering compulsions; (3) saving obsessions with hoarding compulsions; and (4) sexual and religious pre-occupations (Aouizerate et al., 2004).

Selective-serotonin reuptake inhibitors (SSRIs), specifically 5HT-reuptake inhibitor antidepressants, are considered the first line of treatment in OCD (Aouizerate et al., 2004). However, approximately 40-60% of individuals with OCD will experience minimal to no change in symptoms from treatment with SSRIs alone (Goodman, 1999). Cognitive-behavioral therapy is also an important step in the management of OCD, with the primary goal of teaching patients how to respond appropriately to intrusive thoughts in an adaptive manner (Schwartz, 1998).

Psilocybin and other serotonergic psychedelics

Research indicates that serotonin (5-HT) plays an important role in OCD, and that regulation of 5-HT receptors is effective in treating OCD symptoms (Delgado & Moreno, 1998; Wilcox, 2014). Drugs that initiate acute serotonin reuptake inhibition have been shown to reduce obsessive-compulsive symptoms significantly more than other medication (Goodman et al., 1990), and drugs that target the 5-HT_{2A} and 5-HT_{2C} receptors might be particularly effective for longer-lasting symptom remission (Delgado & Moreno, 1998). Psilocybin has established anxiolytic effects (Griffiths et al., 2016; Ross et al., 2016), though most support for its anti-obsessive effects come from case studies.

In one case study, a young man reported a reduction of intrusive thoughts for three weeks after each time he ingested a moderate dose (approx. 2 grams) of psilocybin mushrooms (Wilcox,

2014). As discussed further in the section below on Body Dysmorphic Disorder (BDD), Hanes (1996) reported a case in which a young man's obsessional thinking and mirror-checking significantly decreased after consuming psilocybe mushrooms. One well-known comedian premised his very successful stand-up show on the personal story of using psilocybe mushrooms to treat his refractory OCD⁸.

In an open-label study of psilocybin for OCD (n = 9), participants were administered four doses ranging from low to high, with each dose separated by one week (Moreno et al., 2006). All participants reported a marked reduction in OCD symptoms in at least one dosing session, with improvements generally lasting more than 24 hours. The Moreno et al. (2006) study provides evidence for the safety and tolerability of psilocybin, but more studies must be conducted to determine which dose(s) are most effective for OCD specifically, how long benefits can last, whether a low dose (i.e., non-psychedelic or microdose) is effective, and the role of psychotherapeutic interventions before, during, and after dosing.

Ketamine

Glutamatergic drugs like ketamine are increasingly considered for treatment of OCD symptoms (Dougherty et al., 2018; Pittenger et al., 2011). Both human and animal studies have revealed that people suffering from certain OCD subtypes may have glutamatergic dysfunction (Karthik et al., 2020) and other studies have reported abnormalities in gamma-aminobutyric acid (GABA) in the medial prefrontal cortex (MDFC) (Rodriguez et al., 2015). Therefore, the use of ketamine to regulate glutamate transmission could be an effective therapy because of its role as a noncompetitive inhibitor of the NMDA glutamate receptor and the mechanisms that lead to the enhanced release of serotonin, which has already been discussed as important in OCD pathology. Serotonin reuptake inhibitors are only moderately effective in treating OCD symptoms and there is typically a two to three-month lag before clinical benefits begin, therefore it is worth investigating the role of ketamine as a first-line treatment or as an adjunctive treatment (Rodriguez et al., 2015).

Rodriguez et al. (2015) examined the effects of ketamine on GABA and glutamate-glutamine (Glx) after one IV infusion (0.5mg/kg) and found a significant increase in GABA 60-73 minutes post-infusion, which positively correlated with changes in OCD symptoms. Contrary to expectations, there was no significant increase in Glx levels in the MPFC, indicating a need for more research on the GABAergic mechanism of ketamine and its relation to GABA abnormalities in OCD (Rodriguez et al., 2015).

One clinical trial (Rodriguez et al., 2013) and one open-label study (Bloch et al., 2012) of IV ketamine for OCD reported significant yet transient effects in reducing OCD for up to a week after a single infusion, while one case report (Rodriguez et al., 2011) found relief after two infusions.

⁸ <https://www.themushroomcure.com/>

A case study of intranasal ketamine for OCD yielded no significant effects as well as low tolerability by the patients, who did not like the route of administration (Rodriguez et al., 2017). In another case study, a patient was treated intensively for eight weeks beginning with two weeks of daily cognitive-behavioral therapy (CBT), then three weeks of twice-weekly IN ketamine doses (50mg) in addition to CBT, then twice weekly CBT for one month, then once weekly CBT for one month (Adams et al., 2017). The patient experienced a rapid reduction in suicidality and OCD after the first week, though the treatment was too complex to attribute symptom reduction to the intranasal ketamine alone. However, this case has implications for the efficacy of ketamine-assisted psychotherapy in the treatment of OCD. Rodriguez and colleagues are currently investigating the mechanisms by which ketamine may affect rapid improvement in OCD⁹.

4.3.6 Anxiety and Distress due to Terminal Diagnosis or Advanced Disease

End-of-life distress is identified as a primary reason why individuals pursue medical assistance in dying (Hendry et al., 2013; Salt et al., 2017; Watts et al., 2017). Psychological suffering and existential distress are common among cancer patients approaching end of life and in others experiencing terminal illness. Patients often report feelings of hopelessness, loss of autonomy, social isolation, and demoralization due to loss of a meaningful life (Bauereiß et al., 2018). End-of-life distress is associated with poor treatment and psychological challenges, including decreased medication adherence (Colleoni et al., 2000), diminished quality of life (Colleoni et al., 2000), an increased desire for hastened death, and higher rates of suicide. These factors have been identified as primary reasons for why individuals pursue medical assistance in dying (Salt et al., 2017; Watts et al., 2017). In a study conducted by Fisher et al. (2014), it was found that prevalence of depressive symptoms in palliative care patients was 9.8%. Some risk factors associated with depressive symptoms in palliative care are low life satisfaction, sleep disorders, health instability, caregiver distress, cognitive impairment, gastrointestinal symptoms, and daily pain (Fisher et al., 2014).

LSD

The first publication examining the therapeutic value of psychedelics at the end of life was published in 1964 (Kast & Collins, 1964) and reported that terminally ill patients displayed a cognitive and affective change after ingesting LSD, experiencing a diminished fear of dying. Continued research into the 1970s explored the potential of LSD to alleviate the psychological distress associated with a life-threatening illness by altering the patient's perception of death and their dying condition (Cohen, 1965; Kast, 1966, 1970; Kast & Collins, 1964).

⁹ <https://clinicaltrials.gov/ct2/show/NCT02624596?term=ketamine&cond=Obsessive-Compulsive+Disorder&draw=2&rank=8>

Encouraged by this earlier work, as well as emerging interest in a similar clinical application with psilocybin (see below), Gasser and colleagues (2014) examined the effects of LSD experiences in the treatment of distress related to life-threatening illness. In this Phase 2 clinical trial participants (n = 12) were experiencing anxiety associated with one of several life-threatening diseases, six of whom had cancer diagnoses. Participants received drug-free psychotherapy sessions supplemented by two LSD sessions that were separated by two to three weeks. Each qualifying participant was randomly assigned to receive either 200 (n = 8) or 20 micrograms (n = 3) of LSD in the context of psychedelic-assisted psychotherapy, with the same dose delivered in each of the two sessions. Results showed significant reductions in state anxiety (STAI) at two and 12-month follow-up for the 200-microgram experimental group, but smaller and less persistent effects for the lower dose control group. Gasser et al. (2015) conducted a follow-up analysis of this study 12 months after the participants finished LSD psychotherapy. 10 of the 12 participants completed the follow-up test for anxiety (STAI) and a semi-structured interview. No lasting adverse effects were reported by participants and significant benefits in anxiety reduction (STAI) were sustained over the 12-month period. In a Qualitative Content Analysis (QCA) of the interviews, participants reported reductions in anxiety (78%) and increased quality of life (66%). Drawing on results from the QCA, the authors suggest that, among other mechanisms, LSD facilitated access to emotions and confrontation of previously unknown anxieties, and proposed that intense emotional peak experiences were a major mechanism for therapeutic outcomes (Gasser et al., 2015).

Psilocybin

In 2011, a small pilot study (n = 12) conducted by Grob and colleagues (2011) rejuvenated work in the use of psychedelics to address end-of-life distress by comparing the effects of a moderate dose of oral psilocybin (0.2 mg/kg) and niacin among participants with advanced-stage cancer and clinically significant cancer-related anxiety that met criteria for a DSM-IV anxiety-related disorder. At two weeks follow-up, psilocybin relative to placebo showed a trend toward decreasing severity of depression as measured by the Beck Depression Inventory, and decreased severity of anxiety as measured by the State-Trait Anxiety Inventory. Statistically significant reductions in anxiety symptoms were reported at three months and depressive symptoms at six months.

Two larger studies were subsequently undertaken, both using a substantially higher dose of oral psilocybin (Griffiths et al., 2016; Ross et al., 2016). Griffiths et al. (2016) conducted a Phase 2 clinical trial with 51 patients diagnosed with life-threatening cancer and who met criteria for at least one DSM-IV mood- or anxiety-related disorder in relation to their cancer. Participants underwent two drug administration sessions: one in which a high oral dose of psilocybin (22 or 30 mg/70 kg) was administered, and one in which a very low dose of psilocybin (1 or 3 mg/70 kg) was administered as a comparator condition, with the order of the two conditions counterbalanced across participants. The high psilocybin dose, compared to the very low dose, significantly improved a variety of outcome measures at five weeks after each session. Outcomes on a number of measures remained significantly and substantially reduced at the final six-month follow-up compared to baseline scores, with approximately 60% of participants

showing scores within the clinically normal range, constituting remission. Ratings of mystical experience were significantly associated with a number of clinical outcomes.

Ross et al. (2016) reported on 29 patients with a life-threatening cancer diagnosis who met criteria for a DSM-IV anxiety-related disorder in relation to their cancer. Each participant completed two drug administration sessions. A high oral dose of psilocybin (0.3 mg/kg) was administered in one session, and niacin was administered as a comparator compound in the other. The order of the two conditions was randomized for each participant. Consistent with the results of the larger high-dose study (Griffiths et al., 2016), the high-dose psilocybin condition produced significant improvements on a variety of outcome measures regardless of order of treatment conditions. At approximately six months after treatment, anxiety and depression symptoms remained significantly and substantially reduced compared to baseline scores, with an approximately 60% remission rate for key anxiety and depression outcome measures. Ratings of mystical experience were shown to mediate the relation between psilocybin administration and therapeutic effect of psilocybin on anxiety and depression.

Follow-up interviews with five participants in the Ross et al. (2016) study at one-week post-treatment qualitatively explored the psychological processes underway during and after the psilocybin sessions that may explain the positive outcomes achieved (Belser et al., 2017). Findings revealed the psilocybin experience to be embedded in relationships, for example, forgiveness of others, loved ones as spirit guides, the importance of narrating one's experience with loved ones, and improved post-treatment relationships. Slightly more than half of participants experienced fear or anxiety during the sessions, but the majority came to understand these difficult experiences as part of a necessary and ultimately beneficial process. Finally, participants described lasting impacts on their quality of life, life priorities, and their sense of identity, with descriptions of feeling "reborn," more confident, more connected, and more alive. They also described a feeling of empowerment and being "unstuck," with resulting healthier behaviors.

In a second qualitative study of these same study participants one-year post-treatment, Swift and colleagues (2017) concluded that the experiential and immersive quality of the psilocybin-assisted therapy may help explain the immediate and enduring positive changes in participants' lives after a single session. They noted that participants did not simply return to a pre-cancer diagnosis level of functioning, but rather developed an increased sense of meaning and perspective in their lives.

4.3.7 Psychedelics for Anxiety: Summary

A research team at Monash University in Australia announced in October 2021 the first ever clinical trial to investigate psilocybin-assisted psychotherapy for severe Generalized Anxiety

Disorder. The trial will be randomized and triple-blinded, with an active placebo control and a projected sample size of 72 participants¹⁰.

One known adverse experience associated with psychedelics is transient anxiety related to drug effect onset and the phenomenon of ego-dissolution. Psychedelics for anxiety, however, demonstrate promising early results. Mechanisms of action remain somewhat unclear, but reductions in fear, increased positive affect and therapeutic alliance, memory reprocessing and cognitive flexibility may underlie the ability of psychedelic-assisted therapy to ease symptoms of anxiety disorders.

Apart from ketamine, MDMA-assisted therapy is the most advanced in the process of regulatory drug approval, having recently begun publication of Phase 3 clinical trials. The literature supporting MDMA-assisted psychotherapy for moderate-to-severe or treatment resistant PTSD is compelling, with strong effect sizes and a standardized, manualized approach to therapy. Further Phase 3 trials with more diverse populations and with other therapeutic modalities or approaches to programming is required, especially given the costs associated with extensive psychotherapy required under the current MDMA-AT protocols. In addition, high-dose ketamine in combination with structured therapy may be of benefit in response to TRD and PTSD, though evidence is much less compelling than for MDMA. As noted above, ketamine has further been trialed for social anxiety disorder, anxiety in bipolar disorder, and for anxious symptoms in depressed patients with indications of short-term efficacy, with positive results often dose-dependent and in combination with psychological supports.

Ketamine has demonstrated preliminary safety and tolerability in the treatment of OCD, but efficacy outcomes are mixed and benefits may be quick in onset but transient and not sustained. Conversely, though limited to one published small open-label trial to date, psilocybin for OCD demonstrated safety, tolerability, and preliminary indications of efficacy lasting 24 hours (Moreno et al., 2006).

Psilocybin has proven beneficial in response to distress associated with end of life, with the relevant trials among the most methodologically sound and significant results in reducing depressive and anxious feelings in a dose-dependent manner among patients with advanced cancer diagnoses. Given the humanitarian responsibility to respond to psychological and existential fear and suffering related to palliative care or terminal illness, and the fact that Canadians at present have comparatively ready access to Medical Assistance in Dying (MAID), it seems prudent to further explore the efficacy of potential models for psilocybin-assisted therapy at end-of-life. LSD had previously been shown to be of value at end of life, and contemporary trials to reinitiate this research are warranted. The rapid anti-depressant effects of ayahuasca and DMT, in combination with the spiritual experiences that they occasion, indicate that trials of ayahuasca and/or DMT are also worthy of consideration. The one published survey of treatment response specific to 5-MeO-DMT plus ibogaine for PTSD is suggestive of

¹⁰ <https://www.monash.edu/news/articles/world-first-psilocybin-clinical-trial-in-the-treatment-of-generalised-anxiety-disorder-receives-ethics-approval>

therapeutic effect and warrants clinical investigation. 5-MeO-DMT and DMT may further be possible treatments for depression, as could ibogaine given the known co-morbidity between SUD and depression. Indeed, a derivative chemical of ibogaine known as 18-MC is currently being trialed in a Phase 1, double-blind RCT by the company MindMed for safety and tolerability among healthy volunteers.

Although not discussed in current psychedelic clinical trials, moral injury is a syndrome of biopsychosocial-spiritual suffering resulting from participating, witnessing, or learning about events that transgress one's deeply held moral beliefs (Litz et al., 2009; Shay, 2014) and is associated with significant impairment in relational, health, and occupational functioning (Maguen et al., 2020). Given the indications of effectiveness of MDMA-AT in the treatment of PTSD, and given the relationship between PTSD and moral injury, MDMA trials in the treatment of occupational moral injury in say, for example, health care practitioners during the COVID-19 global pandemic may be of value. Healthcare workers and first responders should also be considered a priority study population, similar to a current trial of MDMA-AT for moral injury among U.S. military veterans (Lehrner & Yehuda, 2021). Indeed, rising concern about burnout, anxiety, PTSD, and depression among healthcare workers in the COVID-19 pandemic has led to the initiation of the first clinical trial of psilocybin-assisted psychotherapy for frontline healthcare workers at the University of Washington¹¹.

4.4 Outcomes Related to Eating Disorders and Body Dysmorphic Disorders

Nearly one million Canadians live with a diagnosable eating disorder such as anorexia nervosa, bulimia, and binge eating. Eating disorders have the highest overall mortality rate of any mental illness, with estimates between 10-15% (Arcelus et al., 2011). Suicide is the second leading cause of death (after cardiac disease) among those with Anorexia nervosa; 20% of people with Anorexia nervosa (Berkman et al., 2007) and 25-35% of people with Bulimia nervosa may attempt suicide in their lifetime (Arcelus et al., 2011). For females aged 15-24 years old, the mortality rate associated with Anorexia nervosa is 12 times greater than all other causes of death combined (Smink et al., 2012). Anorexia nervosa and Bulimia nervosa are conditions notorious for being refractory and/or resistant to treatment, and with long-term complications.

Body Dysmorphic Disorder (BDD) is characterized by extreme distress caused by negative self-perception of an individual's physical appearance, usually of a certain bodily feature, often manifesting as ritualistic, compulsive, and/or avoidant behaviors. BDD is associated with high morbidity and mortality, and shares symptoms with OCD, major depressive disorder, and social phobia (Phillips & Hollander, 2008). First-line therapies for BDD include SSRIs and Cognitive Behavioral Therapy (CBT), with SSRI pharmacotherapy showing high efficacy for treating symptoms. A handful of epidemiological studies have found that the prevalence of BDD ranges

¹¹ <https://depts.washington.edu/clinician-study/>

from 0.7% to 2.4% in the general population (Bjornsson et al., 2010). However, these estimates likely underrepresent the true prevalence of BDD, as affected individuals may feel ashamed of their appearance and neglect to report their BDD symptoms in the clinical context.

Psilocybin

Hanes (1996) reported a case study of a young man suffering from BDD who self-administered psilocybin in conjunction with fluoxetine therapy, suggesting that appropriate pharmacotherapy following the therapeutic use of psilocybin may improve the efficacy of both in mitigating symptoms of BDD and allowing individuals to resume normal social activity. Currently, the New York State Psychiatric Institute in collaboration with Compass Pathways and University of California, Los Angeles is recruiting for a Phase 2 open-label pilot study to administer a single dose of psilocybin to people suffering from BDD who have not responded to at least one adequate trial with SSRIs¹². While there are no completed studies of psilocybin for eating disorders, clinicaltrials.gov reports three trials with psilocybin that are actively recruiting, and one multi-site phase-2 open-label study with MDMA-assisted treatment for eating disorders conducted by MAPS to begin recruitment in 2021.¹³

Ketamine

It has been suggested that eating disorders and BDD are OCD-spectrum disorders, yet both display important differences from OCD (Mills et al., 1998; Phillips et al., 2007). With respect to eating disorders (Anorexia Nervosa and Bulimia Nervosa), Mills et al. (1998) consider them to be a compulsive behavior disorder and as such hypothesize that blocking the excitation of the hippocampus by glutamate-NMDA receptors to stimulate long-term potentiation will reduce memory recall associated with compulsive thoughts and behaviors. Ketamine is known to partially block glutamate-NMDA receptors, therefore Mills and colleagues (1998) administered ketamine with the opioid antagonist nalmeferene (in order to prevent hallucination and loss of consciousness from the ketamine) to 15 patients with eating disorders. Outcomes were measured by a Compulsion score (a 13-item scale based on DSM-III criteria) with subscales for Compulsive Eating, Compulsive Starving, Depression, and Alcohol. Patients were described to be atypical anorexics in that they were chronically treatment-refractory and older than the average eating disorder patient. Nine of the 15 participants responded positively to treatment with a significant and sustained clinical response marked by a return to normal eating behaviors, acceptance of normal weight relative to height, and ease of maintaining social contact. Treatment efficacy was enduring among all responders, varying in time and lasting up to two years of follow-up. Treatment response was associated with a significant decrease in Compulsion scores and Depression scores after ketamine, however the Compulsion score in responders was still significantly higher than the value in controls. The study report provides a detailed account of the recovery trajectory of each participant. Responses to ketamine were

¹² <https://clinicaltrials.gov/ct2/show/NCT04656301>

¹³ <https://clinicaltrials.gov/ct2/results?cond=eating+disorders&term=psychedelic&cntry=&state=&city=&dist=>

dependent on the type of anorexia, bulimia, and whether or not they binged. No serious adverse events were reported; transient side effects included headaches and nausea, both of which were uncommon after the first or second sessions. Limitations to this study are clear: small sample, no psychotherapeutic component, differential eating disorder diagnoses, and use of both nalmefene and amitriptyline during ketamine infusions. Nevertheless, results of this study are promising for further study of ketamine-assisted psychotherapy (KAP) for people with eating disorders.

Despite the relative success of this treatment, no follow-up studies were conducted. More recently, Hermens et al. (2020) explored ketamine in its relation to zinc deficiency in the treatment of Anorexia nervosa noting that controlled studies had provided some limited but positive evidence that zinc supplementation with olanzapine was associated with positive outcomes. Zinc inhibits glutamatergic NMDA receptor functioning and zinc supplementation is associated with increased brain-derived neurotrophic factor (BDNF). Zinc deficiency is linked with lower BDNF (a symptom found among women with AN), and reduced stimulation of gamma-aminobutyric acid (GABA), which may lead to elevated levels of glutamate. Hermens et al. (2020) propose that low-dose ketamine treatment will provide a potent NMDA receptor antagonist that will downregulate excessive glutamate neurotransmission by blocking NMDA reception. Once glutamate transmission is normalized, zinc supplementation can replace the short-term use of ketamine for people with Anorexia nervosa (Hermens et al., 2020).

Following the Mills et al. (1998) study, Schwartz et al. (2021) published a case series to examine the effects of ketamine on depression among people with eating disorders and on symptom severity. Using cases from a study of ketamine for treatment resistant depression, the authors followed four female participants who had been ill with an eating disorder for more than seven years. Three of the four patients exhibited a stabilization of their weight during and in the months after ketamine treatment. The authors reported a clinically meaningful response among this small sample of patients with treatment resistant depression and severe and enduring eating disorders.

Ayahuasca

There is promising early evidence that ceremonial use of ayahuasca may be part of a beneficial therapeutic intervention for people with eating disorders or even as a protective factor against developing disordered eating habits or body dysmorphia. Da Silveira et al. (2005) reported a lower frequency of body dysmorphism among adolescents who drank ayahuasca in the UDV church in Brazil compared to matched controls. LaFrance et al. (2017) conducted a retrospective qualitative exploration of ayahuasca experiences among 16 individuals (14 women, 2 men) with diagnosed eating disorders (anorexia or bulimia). Most participants drank ayahuasca in the context of multi-day retreats conducted in a traditional ceremonial setting, though some described the ceremonial setting as 'eclectic'. 11 of 16 participants reported a reduction of symptoms of their eating disorder, and 14 participants reported significant improvements in emotional regulation and processing. While some of the participants noted concern about the preparatory diet for some kinds of ayahuasca ceremonies (which is common in many Amazonian ayahuasca ceremonial practices and is often restrictive), none of them

reported being triggered by the aspect of the vomiting or other purging that often occurs after consuming the brew. The participants noted that the ceremonial context, safe setting, proper preparation, and integration were key components for maximizing the healing experience and minimizing potential risks. Most participants (14 of 16) received some sort of integration/aftercare support following their ceremonies. This study emphasizes the potential of ayahuasca for recovery from an eating disorder with special attention to various aspects of the setting and aftercare (i.e., integration) as part of the therapeutic process.

Renelli et al. (2020) conducted additional analysis of 13 participants (12 female) from the LaFrance et al. (2017) study to compare perceived experiences and outcomes from ceremonial ayahuasca drinking with their conventional eating disorder treatments. Thematic analysis revealed that participants considered ceremonially ingested ayahuasca to be effective in treating symptoms of eating disorders, particularly due to discoveries of self-love and self-care and the spiritual aspect of healing. Processing unresolved emotions such as grief and shame and emotions associated with painful memories were also cited as significant for recovery. Insights into the 'root cause' of eating disorders were also reported and is consonant with other reports from ayahuasca drinkers about older memories resurfacing either in ceremonies or through post-ceremony dreams. Half of the participants suggested that ayahuasca be combined with psychotherapeutic support and/or conventional treatment for eating disorders. The authors suggest that since symptoms of eating disorders are often tools for self-soothing when confronted with difficult emotions, the ayahuasca experience may offer a context in which to process those emotions on a deeper level than conventional eating disorder treatment, thus highlighting its potential as an adjunctive therapy. Participants reported sustained positive attitudes and behavior in a 14-month follow-up. The study authors noted that people with eating disorders have heightened risks when drinking ayahuasca due to the various physical and mental health complications and comorbidities that are often associated with Anorexia nervosa or Bulimia nervosa such as cardiovascular issues, electrolyte disturbances, the potential contraindicated use of SSRIs and any other MAO-inhibiting medications, and psychological distress during the ceremony. Pre- and post-ceremony dietary restrictions and purging may also be potential triggers for reactivating pathological thoughts and behaviors.

MDMA

An open-label safety and feasibility study of MDMA-assisted psychotherapy is approved by the US FDA for treatment of people with an eating disorder and their treatment allies (e.g., caregivers or partners) (Brewerton et al., 2021). As noted above, MDMA-assisted psychotherapy for PTSD is an experimental therapy that is currently studied in several MAPS-sponsored Phase III clinical trials in Canada, Israel, and the US (MAPS, 2017; Mithoefer et al., 2019). There is an established link between people who suffer from PTSD and people who develop and live with an eating disorder (Brewerton, 2019). Given the well-established safety and efficacy of MDMA-assisted psychotherapy for PTSD, Brewerton et al. (2021) hypothesized that MDMA-assisted psychotherapy may be efficacious for symptoms of both disorders among people with co-occurring eating disorders and PTSD. Brewerton et al. (2022) followed up this hypothesis with results from an exploratory study based on data from the MAPS multi-site Phase III trials in which symptoms of ED were measured with the Eating Attitudes Test 26 (EAT-

26). One of the hypotheses was that a substantial subset of the research participants would score high on the EAT-26, indicating significant ED symptoms, though the study excluded people who were underweight or diagnosed with an ED with active purging to avoid health risks. The other hypothesis was that MDMA-AT would significantly reduce EAT-26 scores compared to placebo-assisted therapy (PLAC-AT). Participants underwent three eight-hour experimental sessions with MDMA-AT or PLAC-AT, spaced four weeks apart with three 90-minute therapy sessions taking place in between experimental sessions. The MDMA group demonstrated significant reductions in EAT-26 scores from baseline to follow-up, which were significantly greater than the PLAC-AT group (-3.04 vs. -0.68, respectively). An analysis of reliable and clinically meaningful change in the total sample determined that these changes were not clinically meaningful for both groups (experimental and placebo). However, analyses of subsets of the total sample with greater baseline EAT-26 scores showed significantly greater improvement at follow-up. The subset with a baseline EAT-26 ≥ 20 demonstrated reliable change in the MDMA group, and clinically meaningful reductions for both MDMA and placebo. The results of this double-blind, placebo-controlled trial indicates that people with severe PTSD and co-occurring symptoms of ED may respond well to MDMA-AT for reducing disordered eating behaviors and thoughts (Brewerton et al. 2022).

4.4.1 Psychedelics for Eating Disorders and Body Dysmorphic Disorder: Summary

There are very few clinical trials concerning the use of psychedelics for eating disorders (ED) and none for Body Dysmorphic Disorder (BDD), yet the existing literature reveals promising potential, in particular for ketamine, ayahuasca, and potentially MDMA. Tentative mechanisms of action have been hypothesized. Early exploratory trials using ketamine demonstrate positive results, clinical trials using psilocybin for eating disorders are currently underway, and retrospective qualitative studies have demonstrated a correlation between ayahuasca ceremony participation and later improvements in eating disorder symptomology. Given the pharmacologic similarities between ayahuasca and other tryptamine-based psychedelics, positive results for ayahuasca could be extended to psilocybin, DMT and 5-MeO-DMT. Much more clinical research is required to provide evidence of efficacy or effectiveness. Current studies investigating psilocybin for Anorexia nervosa are recruiting at Johns Hopkins University¹⁴ and Imperial College, London (Spriggs et al., 2021). A small pilot phase 2 clinical trial at the University of California, San Diego is currently underway examining the safety, tolerability, and efficacy of psilocybin for AN (<https://clinicaltrials.ucsd.edu/trial/NCT04661514>). Patients will receive a single 25mg dose of psilocybin with preparation and integration sessions.

¹⁴ <https://hopkinspsychedelic.org/anorexia> ; <https://clinicaltrials.gov/ct2/show/NCT04505189>

4.5 Outcomes Related to Headache and Pain

Chronic pain is increasingly recognized as a complex disorder associated with significant disability and burden to the affected individual, healthcare system, and society overall (Henry, 2008). Additionally, pain management and alleviation are increasingly seen as a fundamental human right (Brennan et al., 2007). A large population survey of Canadians aged 18 years and older found that 18.9% of respondents reported some form of chronic pain (Schopflocher et al., 2011). That same study found approximately half of those reporting chronic pain had been suffering for more than 10 years. Current pharmacotherapies often have serious adverse effects and are unable to relieve chronic pain for many individuals (Lynch & Watson, 2006). In particular, iatrogenic opioid use disorder is a significant concern and risks the transition by patients to illicit opioid use and thus exposure to a toxic drug supply. Thus, investigation into alternatives is warranted.

Migraine headaches are thought to affect 11% of the world's population (Stovner et al., 2007) and are considered one of the world's most disabling illnesses (Silberstein, 2004). Migraines are caused by increased excitability in the central nervous system (Silberstein, 2004). Pharmacological therapies for the management of migraines include non-steroidal anti-inflammatory drugs, triptans, dihydroergotamine, steroids, and antiemetics (Semenov, 2015).

A cluster headache is a painful, one-sided headache with pronounced cranial autonomic symptoms (such as the flow of tears or conjunctival injection) occurring on the same side of the body (May et al., 2018). It is thought that the hypothalamus is primarily responsible for generating the pain and autonomic symptoms associated with cluster headaches (May et al., 2018). Cluster headaches are not as common as migraines, but they affect approximately one in 1000 adults, with men affected three times as often as women (International Classification Committee of the International Headache Society, 2018). Both migraines and cluster headaches can cause severe pain for affected individuals, such that many are unable to participate in school, work, social activities, and family life, thus causing a significant economic and societal burden (Silberstein, 2004).

Ketamine

There are several case studies and case series concerning the use of ketamine for the treatment of chronic pain related to depression, cancer, and/or suicidality (Chang et al., 2010; Iacobucci et al., 2017; Mischel et al., 2018; Romero-Sandoval, 2011; Sexton et al., 2018). Because we address ketamine-assisted treatment for depressive disorders and suicide in previous sections, these studies will not be recapitulated here.

Ketamine may be effective for pain disorders, including chronic migraine and cluster headaches (Chizh, 2007). Ketamine is known for its analgesic effects, yet the mechanisms of action are still unclear and evidence for ketamine in the use of migraine and cluster headaches is limited. Glutamate is considered an important neurotransmitter in migraine pain and central sensitization (Hoffman & Charles, 2018). Glutamate levels are higher in the brains of patients with migraines, particularly during a migraine episode (Hoffman & Charles, 2018). NMDA antagonists, such as

ketamine, block glutamate and excitatory neurotransmission. Moisset et al. (2017) report two case studies of men with cluster headaches who experienced full and partial relief for six weeks after a single infusion of ketamine combined with magnesium sulfate.

Pomeroy et al. (2017) conducted a retrospective analysis of 77 patients (57 female, mean age 40.6) with chronic migraine or new daily persistent headache. Most patients had multiple comorbidities, and all had demonstrated refractory chronic headache disorders that had failed aggressive treatments. Patients were administered subanesthetic IV ketamine in a hospital setting, with infusion length varying from two to nine days, mean 4.8 days. Based on at least a two-point improvement in the verbal pain rating scale, 55 (71.4%) patients were classified as acute responders, among which 15 (27.3%) were sustained responders at follow-up, however the follow-up confidence interval did not achieve significance. Adverse events were reported to be generally mild and were resolved by decreasing the ketamine dose. The authors suggest that IV ketamine provides acute relief for a highly refractory population with chronic migraine or new daily persistent headache but do not recommend it as a preventative treatment nor suggest that the results generalize to more typical (i.e., less refractory) cases (Pomeroy et al., 2017). In addition to the open-label and retrospective design of the study, another limitation was that other treatments were sometimes used along with ketamine, thus limiting the ability to determine the efficacy of ketamine on its own for this condition.

Lauritsen et al. (2016) also reported transient improvement in migraine pain severity in a retrospective case study. Intranasal ketamine may reduce or stop pain in prolonged migraine with aura (Afridi et al., 2013; Kaub et al., 2000) and may be effective for neuropathic pain as well (Huge et al., 2010). A systematic review and meta-analysis found that IV ketamine provided significant short-term (approximately two weeks) relief in patients with refractory chronic pain (Orhurhu et al., 2019). Both intravenous and intranasal ketamine were considered well-tolerated by patients. A systematic review of 10 studies found that intranasal ketamine and intranasal esketamine were effective for acute pain in the emergency department but were not more effective than other drugs and were associated with more undesirable effects (Rocchio & Ward, 2021).

Serotonergic psychedelics

One clinical trial has been completed investigating the safety and efficacy of psilocybin in the treatment of migraine headaches (Schindler et al., 2021). This exploratory controlled study (n = 10) found a reduction in weekly migraine days throughout the two-week follow-up period after a single dose of psilocybin. This trial used the lowest dose of psilocybin (0.143mg/kg) compared to a more common investigatory dose of 0.3mg/kg of any yet-published psilocybin clinical trial. Investigators found no correlation between intensity of subjective drug effects and enduring therapeutic outcomes. There were no serious adverse events and psilocybin was well-tolerated.

Several case series, qualitative, and retrospective studies have reported improvements among patients with cluster headaches and migraine (Andersson et al., 2017; Karst et al., 2010; Sewell et al., 2006), phantom limb pain (Fanciullacci et al., 1977; Ramachandran et al., 2018), and neuropathic pain (Kast & Collins, 1964) associated with use of psilocybin, LSD, or a

combination of both. The Ramachandran et al. (2018) case study of phantom limb pain relief suggests the potential for psychedelic-assisted treatments combined with other modalities, in this case mirror visual-feedback. A survey of 496 cluster headache patients reported that indoleamine hallucinogens (psilocybin, LSD, LSA) were perceived to shorten or abort a cluster period and bring chronic cluster headaches into remission more so than conventional medications (Schindler et al., 2015). Respondents generally found that these substances were comparably or more efficacious than preventive and abortive medications. Schindler et al. (2015) claim that no other single drug has been reported to halt attacks, induce remission, *and* prolong the duration of remission. In a review of psychedelics for chronic pain, Castellanos et al. (2020) suggest that the 5-HT_{2A} receptor agonism might work to ‘reset’ functional connectivity in brain areas with a central role in neuropathic states. Further, the authors suggest the 5-HT_{2A} receptor may have an important role in the inflammatory response, hyperalgesia, and neuropathic pain. Stimulation of certain 5-HT receptors by LSD and psilocybin may have antinociceptive actions (Whelan & Johnson, 2018). In addition to direct action on nociceptors, there may be a perceptual advantage in that chronic pain disrupts processing in the default-mode network, thus the DMN-inhibitory action of mindfulness training and serotonergic psychedelics may influence activity in brain regions linked to chronic pain (Whelan & Johnson, 2018). Serotonergic psychedelics such as ayahuasca/DMT and LSD are known to increase brain-derived neurotrophic factor, which co-regulates glutamate. Since metabotropic glutamate receptors (mGluRs) modulate pain transmission (Pereira & Goudet, 2019), this may be a mechanism of action for serotonergic psychedelics as well as ketamine.

A clinical trial of lose-dose LSD among healthy volunteers (n = 24) found that at 20µg doses participants reported a decrease in pain perception (Ramaekers et al., 2021). Researchers at University Hospital in Basel, Switzerland are currently recruiting for the first clinical trial of LSD for chronic pain in 40 years¹⁵. Several studies of psilocybin for neuralgiform headache, post-traumatic headache, cluster headache, and migraine headache are being conducted in the US, UK, and Denmark¹⁶.

4.5.1 Psychedelics for Headaches/Migraine and Chronic Pain: Summary

Case studies indicate ketamine may be effective for pain disorders, including chronic migraine and cluster headaches, but clinical trials are required to provide evidence for efficacy and tolerability. Serotonergic psychedelics hold promise with several case series, qualitative, and retrospective studies which have reported improvement in cluster headaches and migraine, phantom limb pain, and neuropathic pain with psilocybin, LSD, or a combination of both. One clinical trial has documented enduring therapeutic effects as measured by reductions in migraine frequency after a single dose of psilocybin. Additional trials that are sufficiently

¹⁵ <https://clinicaltrials.gov/ct2/show/NCT03781128?term=psychedelic&cond=pain&draw=3&rank=13>

¹⁶ <https://clinicaltrials.gov/ct2/results?cond=headache&term=psychedelic&cntry=&state=&city=&dist=>

powered and methodologically rigorous are required to establish safety, tolerability, efficacy, and effectiveness. Underlying neurobiological mechanisms of action have been proposed and require further research.

4.6 Other Health and Mental Health-related Conditions

4.6.1 Autism Spectrum Disorder (ASD)

Autism Spectrum Disorder (ASD) is an umbrella term used to describe early-onset social deficits and repetitive sensory-motor behaviors (Lord et al., 2018). The spectrum includes several related conditions: autistic disorder, Asperger syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (Sanchack & Thomas, 2016). These individuals typically have very restricted interests and activities (Sanchack & Thomas, 2016). An estimated 1 in 66 children and youth (5-17 years of age) in Canada were diagnosed with ASD in 2015 (Public Health Agency of Canada, 2018). ASD affects approximately 1-2% of the global population and often co-occurs with depression, anxiety, and impaired social behavior and communication (Chiarotti & Venerosi, 2020).

While many affected individuals are able to live in the community with very few remaining symptoms by adulthood, some individuals will not be able to work full-time or live independently (Lord et al., 2018). There is no consensus on the underlying pathophysiology of ASD, however the fields of genetics and neuroscience are continuously advancing our understanding of the condition. Currently, there is no medication to treat the causes of ASD (LeClerc & Easley, 2015) and there are no selective treatments that target core ASD traits such as irritability, anxiety, and depression, thus these are often addressed with antipsychotics, antidepressants, mood stabilizers, and stimulants (Markopoulos et al., 2022).

The history of psychedelic treatment of autism reaches back to 1959 in a study of LSD for children with autism, when the condition was considered a manifestation of schizophrenia (Sigafoos et al., 2007). From 1959 to 1970, dozens of trials to ‘treat’ autistic children with LSD, UML¹⁷, and psilocybin were conducted in the US, Europe, and Argentina (Danforth et al., 2016; Sigafoos et al., 2007). These studies were ethically questionable and methodologically flawed. New studies of psychedelic-assisted therapy for people with autism do not aim to ‘treat’ or ‘cure’ autism, but to help autistic adults cope with anxiety, depression, social phobia, reduced communication skills, and lack of social connectedness (Danforth et al., 2016).

As mentioned, MDMA has been approved by the US FDA as a ‘breakthrough therapy’ for psychotherapeutic treatment of PTSD. A systematic review of human and animal studies concluded that MDMA should be a clinically approved drug for managing many of the core impairments experienced by people with ASD (Chaliha et al., 2021). The observed effects of

¹⁷ 1-Methyl-D-Lysergic Acid Butanolamide

MDMA on mitigating anxiety disorders and social anxiety (Johansen & Krebs, 2009) and augmenting emotional reading and perceptions of increased closeness (Hysek et al., 2014) has stimulated interest in its ability to help people with ASD. The serotonergic effects may increase a sense of calm and elevated peripheral plasma levels of oxytocin stimulated by MDMA is positively associated with prosocial feelings, which is theorized to be part of the complex pharmacology that leads to improved feelings of empathy, connectedness, and ease of communication (Danforth et al., 2016).

A randomized, double-blind, placebo-controlled trial with two eight-hour MDMA-assisted psychotherapy sessions showed positive results in reducing social anxiety at study completion and six-month follow-up in autistic adults with moderate to severe social anxiety (Danforth et al., 2018). An international mixed-methods inquiry into MDMA experiences among autistic adults reported that 91% of survey respondents (n = 100) felt increased feelings of empathy/connectedness and 86% reported ease of communication. In the qualitative component (n = 24), themes included citing MDMA for immediate as well as transformational change (i.e., long-term changes), and as a catalyst for healing (e.g., improved self-esteem/self-image, anxiety, difficulties with communication). Markopoulos et al. (2022) review the evidence for the therapeutic potential of psychedelic compounds in the treatment of core features of ASD, concluding with highly cautious optimism that certain psychedelics may improve social behavior and relieve social anxiety and other co-occurring diagnoses. While the authors suggest further research is warranted, they are careful to note the many ethical challenges of working with such a diverse demographic, some of which are children and/or have intellectual disabilities.

One current clinical trial of MDMA-assisted therapy for people with ASD is investigating its role in responses to affective touch¹⁸.

4.6.2 Personality Disorders

Zeifman and Wagner (2020) recently reviewed the potential of psychedelic-assisted psychotherapy for borderline personality disorder (BPD). People with BPD struggle with emotional dysregulation, behavioral dysregulation, disturbances in self-identity, and social functioning. First-line treatment is an array of psychotherapeutic techniques and there is no recommended pharmacological intervention. Considering the mounting evidence for psychedelics' efficacy in targeting a variety of symptoms and conditions that overlap with BPD, Zeifman and Wagner (2020) make the case for studying the direct impact of psychedelics such as psilocybin, LSD, ayahuasca, MDMA, and ketamine on the many challenging aspects of BPD cited above.

Ayahuasca is known to promote mindfulness and may even aid in enhancing skills such as decentering, acceptance, non-reacting, non-judging, and emotional regulation (Domínguez-Clavé et al., 2018). Domínguez-Clavé et al. (2018) conducted a naturalistic study of 45

¹⁸ <https://clinicaltrials.gov/ct2/show/NCT04053036?term=MDMA&cond=autism&draw=2&rank=2>

ayahuasca drinkers, 12 of which exhibited BPD-like traits, to explore its effect on improving emotional regulation, which is a core characteristic of BPD. Participants drank ayahuasca in a group ceremonial context in Barcelona, Spain. Significant pre-post differences in emotional regulation were observed in both groups (with / without BPD-like traits), as were positive effects of ayahuasca on mindfulness-related capacities. Given the positive results, the lack of any adverse effects during or after ceremonies, and the lack of an indicated pharmacological treatment for BPD, ayahuasca may hold promise for people with BPD. Unlike other psilocybin clinical trials, a clinical trial to ameliorate demoralization among long-term AIDS survivors did not exclude candidates with BPD ($n = 2$ of 18) and reported positive therapeutic outcomes, though increased difficulty, for this patient population (Anderson et al., 2020a).

4.6.3 Schizophrenia

Schizophrenia is considered one of the most severe and debilitating psychiatric disorders, with symptoms including hallucinations, delusions, a lack of motivation, and a lack of speech (Schultz & Andreasen, 1999). One out of 100 Canadian individuals 10 years of age or older are living with diagnosed schizophrenia (Public Health Agency of Canada, 2020). Interestingly, a systematic review found significantly higher prevalence and incidence rates of schizophrenia in Canada compared to other countries (Dealberto, 2013).

The pathophysiology of schizophrenia is not yet fully understood, and current antipsychotics are only effective in approximately half of affected patients (Stepnicki et al., 2018). Additionally, antipsychotics typically only resolve positive symptoms such as hallucinations and thought disorders, and they involve severe neurological and metabolic side effects (Stepnicki et al., 2018). There is a need for alternative pharmacotherapies that can address the negative and cognitive symptoms with less severe side effects.

In 2001, Dr. Julie Holland (Holland, 2001) posited the potential benefits of MDMA for helping people with schizophrenia to cope with their illness. MDMA-assisted psychotherapy may help in temporarily reducing acute symptoms, allowing the individual to explore long-term recovery or symptom management strategies. Although some investigators show interest in exploring psychedelics for schizophrenia-spectrum disorders, it is generally considered contraindicated for psychedelic use and most clinical trials to date have used a history of schizophrenia as part of the exclusion criteria.

4.6.4 Grief

Grief describes the overwhelming emotional suffering that occurs in response to loss (Mughal et al., 2021). Grief-related stress can lead to high blood pressure, tachycardia, and increased blood cortisol levels (Mughal et al., 2021). It may induce disruption of cholesterol-filled plaques lining coronary arteries and cause constriction of blood vessels, thus increasing the risk of myocardial infarction (Mughal et al., 2021). In severe cases, takutsubo cardiomyopathy may occur, which causes the adrenal glands to produce excessive levels of adrenaline, thus reducing blood flow to the heart (Akashi et al., 2008). Most persons adapt to normal grief over

six months to two years; however, complicated grief may require pharmacological therapy in combination with grief therapy (Iglewicz et al., 2020). Citalopram is often used in combination with interpersonal therapy (Mughal et al., 2021), however a study found that adding citalopram to psychotherapy for complicated grief did not significantly improve overall outcomes from complicated grief treatment but did result in a significant decrease in depressive symptoms (Shear et al., 2016). Thus, alternative approaches are needed to ameliorate severe and enduring grief and its health complications.

Ayahuasca

One exploratory observational study (González et al., 2017; n = 30) and a one-year follow-up to that same study (González et al., 2020; n = 50) found significant reduction in grief associated with the death of a first-degree relative (parent, sibling, spouse, child) after participating in traditional ayahuasca ceremonies at an Amazonian ayahuasca retreat center. In the mixed-methods observational study, González et al. (2017) compared the ayahuasca-drinking participants with 30 people who had attended peer support groups and found that people who drank ayahuasca had lower reported levels of grief than the comparison group. Significant reported themes from ayahuasca drinkers included emotional release, biographical memories, and contact with the deceased, all of which were reported to be helpful in bereavement acceptance and letting go (González et al., 2020). In the follow-up study, participants (n = 50) at the same retreat centre submitted a questionnaire five days prior to the retreat, then 15 days, 3 months, 6 months, and 12 months post-retreat. They found that the severity of grief significantly reduced after the retreat, and this was maintained over the one-year follow-up period.

These are the only studies concerning ayahuasca for grief and there are no studies we are aware of that report the effects of other psychedelics for the grieving process. The journalist Michael Pollan (2018) has famously written about his own use of psychedelics in grieving the death of his father and other authors have similarly written about the usefulness of psychedelics in the grieving process, both at larger doses and microdoses (Anonymous, 2019; Preston, 2021).

4.6.5 Alzheimer's, Dementia, and Neurocognitive Disorders

Psychedelics such as LSD and psilocybin have been implicated in provoking neuroplasticity and reducing inflammation (Vann Jones & O'Kelly, 2020). Alzheimer's Disease (AD), which accounts for at least half of reported dementia cases, is widely thought to be caused by the buildup of amyloid plaque and is also associated with a deficit of serotonergic neurons, which likely worsen the downregulation of acetylcholine signaling that characterizes patients with AD (Kandimalla & Reddy, 2017; Rodriguez et al., 2012). Since psychedelics like LSD and psilocybin are serotonergic drugs, they may have similar beneficial effects as SSRIs in improving memory impairment and decreasing inflammation (Ma et al., 2017). AD and other neurodegenerative disorders are also characterized by chronic inflammation (Kinney et al., 2018). Serotonergic psychedelics have been shown to have anti-inflammatory effects (Flanagan & Nichols, 2018; Galvão-Coelho et al., 2020; Yu et al., 2008) and one double-blind, placebo-controlled study has

demonstrated the safety and tolerability of low-dose LSD among healthy older adults and its implications for AD treatment (Family et al., 2020). Experts in the field of psychedelic pharmacology consider further research into psychedelics for inflammation, Alzheimer's and dementia, and other neurodegenerative disorders to be high priority¹⁹ (Aday et al., 2020; Cini et al., 2019; Family et al., 2020; Kuypers et al., 2019). The London and New York-based company Eleusis is conducting research on the therapeutic potential of LSD for Alzheimer's disease²⁰ and on serotonergic-based psychedelics for inflammation. Ketamine is also considered a potential therapy for AD. Although many studies have investigated the anti-depressive effects of ketamine in people with AD, there are no known studies that investigate the effects of ketamine directly on AD (Smalheiser, 2019). Despite this, the company Alkido Pharma, Inc., has filed a patent for the use of ketamine to treat Alzheimer's disease and existing ketamine clinics already advertise the potential of ketamine for AD (e.g., <https://tahoeketamine.com/ketamine-and-alzheimers-disease/>).

4.6.6 Traumatic Brain Injury

Traumatic brain injury (TBI) is the most common cause of long-term disability and death in young adults (Hackenberg & Unterberg, 2016), and thus is associated with a high socio-economic and healthcare burden. Swelling in the brain increases intracranial pressure, thus reducing cerebral perfusion pressure and blood flow (Hackenberg & Unterberg, 2016). The global incidence of all-cause, all-severity TBI is estimated to be 939 cases per 100,000 people each year (Dewan et al., 2019). In Canada, TBIs occur at an annual rate of 500 per 100,000; 2% of the population lives with a TBI and there are 18,000 hospitalizations for TBI each year, warranting the term 'silent epidemic' (Brain Injury Canada, 2022).

Research has demonstrated the effectiveness of ketamine in suppressing spreading depolarization after a traumatic brain injury (Carlson et al., 2018). Since depolarization occurs in the majority of TBI patients and is associated with worse outcomes, therapies such as ketamine may be important for improving recovery.

There is anecdotal evidence for the use of ayahuasca and psilocybe mushrooms for traumatic brain injury by professional athletes who advocate for clinical research on this topic²¹. They report reduced depression and anxiety as well as complete remission of headaches, memory issues, and insomnia. Khan et al. (2021) reported on what they referred to as a narrative "mini review" of psychedelics for stroke and TBI and noted that historical data from *in vitro*, *in vivo*, and case studies provide evidence for their safety, prompting the authors to advocate phase 2 trials to further investigate mechanisms and efficacy (Khan et al., 2021). Scott and Carhart-

¹⁹ <https://clinicaltrials.gov/ct2/show/NCT04123314?term=psilocybin&cond=Alzheimer+Disease&draw=2&rank=1>

²⁰ <https://www.eleusisltd.com/science/>

²¹ <https://www.forbes.com/sites/amandasiebert/2020/11/26/these-four-former-pro-athletes-are-using-psychedelics-to-heal-their-brain-injuries/?sh=4727f5ba70d7>

Harris (2019) advocate for the use of psychedelics as a treatment for disorders of consciousness after serious brain injury. Disorders of consciousness are forms of impairment that may follow brain injury, defined as vegetative states, locked-in syndrome, minimally conscious states, or chronic coma, in which individuals show minimal signs of wakefulness or awareness. Scott and Carhart-Harris (2019) argue specifically for exploring the use of psilocybin to increase conscious awareness based on the logic that psychedelics increase brain complexity, which is a reliable index of conscious level.

4.6.7 Well-being, Cognition, Mindfulness, and Creativity

Clinical research on mental health and substance use typically focus on specific mental disorders as defined by the DSM, their symptoms, and related co-morbidity. However, this pathology-focused agenda is complemented by research that investigates activities and interventions aimed at improving or maintaining overall well-being and preventing mental illness or cognitive decline in healthy individuals. Such activities and interventions often include a balanced diet (i.e., healthy gut microbiome), physical activity, time in nature, creative pursuits, and meditation or mindfulness practices. The use of psychedelics has long been reputed to enhance well-being or contribute to the ‘betterment of well people’ through various mechanisms that have already been discussed such as their anti-inflammatory effects, their prosocial effects, their serotonergic and dopaminergic effects. Other mechanisms include enhanced perceptions of connectedness with nature and with other people (Carhart-Harris et al., 2018b; Gandy et al., 2020; Kettner et al., 2019), transient increased mindfulness, decentering, and cognitive flexibility (Murphy-Beiner & Soar, 2020; Soler et al., 2018), and induction of experiences of wonder and awe (Tupper, 2011; Hendricks, 2018). Tupper suggests that psychedelic and entheogenic experiences have potential educational value as cognitive tools for learning about the self and one’s environment, as well as cultivating existential intelligence (Tupper 2002, 2003). Thus, while psychedelics show promise for select primary and secondary healthcare issues, there is also potential for their use in preventative medicine and as a tool to promote overall wellbeing, even education, both among healthy people and those living with chronic conditions.

Anderson et al. (2020a) assessed the impact of psilocybin-assisted group therapy on outcomes associated with demoralization among long-term AIDS survivors. Demoralization is a form of existential suffering characterized by poor coping and a sense of helplessness, hopelessness, and a loss of meaning and purpose in life. In an open-label safety and feasibility pilot study they recruited self-identified gay men (n = 18) to participate in 8-10 group therapy sessions combined with one psilocybin administration session (0.3-0.36 mg/kg po). Feasibility and safety were assessed according to rates of participant recruitment, participant retention, and adverse events. The primary clinical outcome was change in mean demoralization, measured by the Demoralization Scale-II, at baseline, end-of-treatment, and at three-month follow-up. A clinically meaningful change in demoralization was observed at the three-month endpoint, indicating the potential role of group therapy within a psychedelic-assisted therapy paradigm. No serious adverse reactions were reported, although two unexpected adverse reactions and seven self-limited severe expected adverse reactions were reported. The results of this small, open-label

pilot study suggest that psilocybin-assisted therapy in a group setting may contribute to improved well-being among adults living with chronic illness.

Mental health-related factors such as wellness, creativity, and cognitive flexibility are currently being explored in clinical research. Further, there is a growing body of naturalistic/observational research drawing upon the experience of those who have used psychedelics in a wide range of contexts. The following paragraphs summarize studies concerning various psychedelics in both clinical and naturalistic settings.

5-MeO-DMT

Limited investigations into the naturalistic use of synthetic and toad-derived 5-MeO-DMT have yielded promising insights about its potential for enhancing well-being. Uthaug et al. (2020) report that study participants who inhaled vapor from synthetic 5-MeO-DMT had significant changes in inflammatory markers, improved affect, and non-judgement. After a single inhalation of dried toad secretion containing 5-MeO-DMT in a naturalistic setting, participants reported increased subjective ratings of satisfaction with life, non-judgement, and awareness (Uthaug et al., 2019).

Ayahuasca

The study of ayahuasca drinkers who participate in Brazilian syncretic churches (e.g., Santo Daime, UDV, Barquinã) provided the first insights into the potential value of ayahuasca for mental health outcomes, broadly speaking. Grob et al. (1996) initiated this research with a case-control design and showed that long-term regular members of the UDV reported less psychopathology and better memory function than matched controls, community members who had never drunk ayahuasca. Two similarly designed studies compared adolescent users in the UDV with a matched control group, reporting lower incidence of some psychiatric symptoms (e.g., depression, anxiety, attentional problems) and alcohol use among the ayahuasca-using group, but no difference in neurocognitive functioning (Da Silveira et al., 2005; Doering-Silveira et al., 2005). Barbosa and colleagues (2009) compared performance on a variety of measures of psychological functions among ayahuasca-naïve participants (i.e., adult first time users; $n = 23$) in Santo Daime ($n = 15$) or UDV ($n = 8$). At six-months after their first ayahuasca experience significant pre-post differences were noted in intensity of minor psychiatric symptoms, improvement in mental health and an increase in confidence and optimism. A sub-group reported a reduction in somatic pain. Some but not all of the mental health outcomes were associated with intensity of use, suggesting that a particular number of sessions conducted in specific intervals may optimize benefits. Three recently reported studies explored a variety of mental health outcomes associated with ayahuasca drinking in a broad ceremonial context beyond the Brazilian syncretic churches. Kiraga et al. (2021) asked volunteers who attended ayahuasca ceremonies ($n = 43$) in the Netherlands between 2017-19 to complete a battery of measures at baseline, the morning after, and one-week post-ceremony. At the one and seven-day mark post-ceremony, cognitive empathy, satisfaction with life, and decentering increased while divergent thinking decreased compared to baseline.

Ona et al. (2019) took an innovative approach to the study of mental wellness by comparing a large sample of ritual ayahuasca drinkers in Spain on a variety of health measures drawn from public health “scorecards”. Participants in ayahuasca ceremonies ($n = 380$) scored higher than the population norm on a wide range of common public health indicators (e.g., perceived health status, level of cholesterol and hypertension, prevalence of chronic disease). More than half of the participants reported reducing their use of medical and/or mental health services due to ayahuasca use, including their use of prescription medication.

Kaasik and Kreegipuu (2020) matched 30 ceremonial ayahuasca drinkers in Estonia to a group of non-drinkers and reported lower scores on a variety of screening test indicators of depression and anxiety. Mostly positive subjective consequences were reported for their overall health and wellness, although some challenging experiences and adverse effects were also reported. No deterioration in mental health status of ayahuasca drinkers in comparison to non-drinkers was noted.

Ayahuasca drinkers have been shown to score high in ratings of Decentering and Positive Self (Franquesa et al., 2018). In a single-blind, placebo-controlled naturalistic study among experienced ayahuasca drinkers (mean = 23.7 times, SD = 15.8) at six retreat locations in Europe, participants were given ayahuasca ($n = 14$) or placebo ($n = 16$) in a ceremonial setting (Uthaug et al., 2021b). Most participants took either freeze-dried ayahuasca or placebo capsules, though in one location they drank ayahuasca brew or placebo. Both groups exhibited significant decreases from baseline in stress, anxiety, and depression as measured by the Depression, Anxiety, and Stress Scale 21, indicating that the ceremonial context and other non-pharmacological factors involved in ayahuasca ceremonies may improve overall feelings of well-being. However, this study had significant methodological flaws, not least of which was a problematic low dose of the active ayahuasca, thus making it impossible to draw firm conclusions. Further rigorous studies of ayahuasca in a ceremonial setting are warranted for investigating effects on well-being.

Psilocybin

Johnson et al. (2017b) conducted an online survey to assess factors associated with tobacco cessation and naturalistic use of psychedelics, a large proportion (43.7%) of whom reported on their tobacco-related experience with psilocybin. Psychedelic use, including among this sub-sample, was significantly associated with smoking cessation and/or reduction of use. Consistent with a previous clinical pilot study, the personal meaning and spiritual significance of the experience was associated with non-relapse. Participants across all sub-groups of quitters and relapsers reported less severe withdrawal symptoms associated with smoking cessation or reduction; further, changes in life priorities/values were endorsed as the most important psychological factor associated with both cessation and reduction.

In a follow-up of a pilot study on the efficacy of psilocybin for cessation of tobacco use, benefits identified beyond tobacco cessation at 30 months included aesthetic appreciation, altruism and pro-social behaviour (Noorani et al., 2018). As noted earlier, follow-up of participants in clinical trials of the efficacy of psilocybin for relieving end-of-life psychological distress revealed lasting

impacts to their quality of life, life priorities, and their sense of identity, including feelings of being “reborn,” more confident, more connected, and more alive (Belser et al., 2017). Participants also described a feeling of empowerment and being “unstuck,” which were associated with resulting healthier behaviors.

Psychedelics and wellness: Reports from large-scale surveys

Many of the findings from relatively small samples of ritualistic ayahuasca drinking and clinical studies with psilocybin are replicated in large-scale community surveys. Larger-scale surveys of healthy community members have offered a unique perspective on the reasons for, and expectancies associated with, psychedelic use, as well as its perceived benefits and risks. A number of online surveys have compared well-being, substance use, and other factors associated with life satisfaction among users of different psychedelics. An online, self-selecting, global survey conducted in 2015 and 2016 (n = 96,901) asked questions about use of ayahuasca, LSD, and magic mushrooms (psilocybin), current well-being, and past-year problematic alcohol use (Lawn et al., 2017). In addition to less problematic alcohol use (noted in an earlier section of this report), ayahuasca drinkers (n = 527) reported greater well-being than both classic psychedelic users (n = 18,138) and non-psychedelic drug-using respondents (n = 78,236). Studies of long-term ayahuasca users among members of the Brazilian syncretic churches also show reduced indices of psychopathology and increased psychological wellbeing (Bouso et al., 2012).

In a broad Internet-based survey, Griffiths et al. (2019) found that, compared to those using other psychedelics such as LSD, psilocybin, or DMT, ayahuasca users in the general population reported mystical experiences to be more positive and with more enduring impact on life satisfaction, social relationships, spiritual awareness in everyday life, and attitudes about life and self, mood, and behaviour. As a possible explanation for this more enduring impact, the authors pointed to the common format for ayahuasca use in a structured religious or spiritual group context.

Krebs and Johansen (2013) and Johansen and Krebs (2015) reported on data from years 2001 to 2004 of the US National Survey on Drug Use and Health and confirmed that use of psychedelics was not an independent risk factor for any mental disorders or mental health problems, including serious psychological distress, mental health treatment, suicidal thoughts, suicidal plans, and suicide attempts.

Hendricks et al. (2015b) went on to evaluate the relationships of classic psychedelic use with psychological distress and suicidality among over 190,000 USA adult respondents pooled from the last five available years of the National Survey on Drug Use and Health (2008–2012), controlling for a range of covariates. Lifetime classic psychedelic use was associated with a significantly reduced odds of past-month psychological distress, past-year suicidal planning, and past-year suicide attempt, whereas lifetime illicit use of other drugs was largely associated with an increased likelihood of these outcomes. These findings indicate that classic psychedelics may hold promise in the prevention of suicide. Subsequent analyses reported by Hendricks et al. (2015a) confirmed the protective association with psilocybin specifically, and further, that the

association found in the initial study held true only for psilocybin among all members of the overall class of hallucinogens included in the survey.

In a Canadian study, Argento et al. (2017) reported similar findings in a longitudinal assessment of predictors of suicidality among community sex workers. Results showed a *protective* association between self-reported lifetime use of one or more classic psychedelics and initiation of suicidal ideation. Previous use of all other illicit drugs was associated with a higher risk of suicidality; only psychedelics showed a protective effect. Further analyses showed that psychedelic use also had a protective moderating effect on the relationship between prescription opioid use and suicide risk.

Recently, Perkins et al. (2021) reported results from the Global Ayahuasca Project for a subset of respondents who had drunk ayahuasca with two or fewer groups ($n = 6877$). Participants from 40 countries were sub-categorized as having used in traditional (i.e., shamanic), religious, and non-traditional settings. Taking advantage of the large sample size, the analytic focus was to assess associations between ritual-ceremonial characteristics, additional support practices, patterns of prior ayahuasca use, and measures of mental health and wellbeing. Mental health measures included perceived growth in psychological wellbeing; current mental health status (SF-12); current level of psychological distress (K-10); and perceived change in prior clinical diagnoses of anxiety or depression (Global Impressions of Change). In a multivariate model, these mental health measures were associated with a wide range of set and setting-related variables including motivations for participation (i.e., seeking therapeutic support); perceived safety and support; and preparation activities. The number of times ayahuasca was used was also positively associated with the mental health and wellbeing measures.

Based on the same global survey, Sarris et al. (2021) focused on those participants who had reported a diagnosis of depression ($n = 1571$) or anxiety ($n = 1125$) at the time of consuming ayahuasca. 78% reported that their depression was either “very much” (46%) or “completely resolved” (32%), while 70% of those with an anxiety diagnosis reported their symptoms as “very much improved” (54%) or “completely resolved” (16%). A range of factors were associated with greater symptom improvement, including subjective mystical experience, number of ayahuasca sessions, and number of personal psychological insights experienced. Importantly, 2.7% and 4.5% of users with depression or anxiety, respectively, reported worsening of symptoms.

To summarize briefly, aside from the importance of diagnostic-oriented outcomes in the field of psychedelic science, other mental health and substance use-related outcomes are also of high interest. These include topic areas such as mental wellness, life satisfaction, empowerment, demoralization, quality of life, and so on. These domains are equally important in addition to the application of psychedelic-assisted therapies for people with clinical diagnoses (see, for example, Thornicroft & Tansella, 2010). The fairly large body of naturalistic and observational studies demonstrate the importance of wellness-focused outcomes to complement clinical research, such as the Anderson et al. (2020a) study of demoralization among long-term AIDS survivors. Naturalistic studies are also significant for highlighting researchers and study populations that bring an Indigenous worldview to psychedelic therapies, given the holistic

nature of views on health and wellness that are integral to traditional practices. For further discussion on study design and diversity in methodologies, see section 6.2.2.

5.0 Microdosing

Microdosing refers to the periodic regular consumption of very small/functionally low doses of psychedelic compounds (such as *Psilocybe* mushrooms or LSD). Typically, a microdosing regimen involves taking one-tenth to one-twentieth of regular psychedelic doses at specific intervals for purported health or psychological benefit (Johnstad, 2018; Kuypers et al., 2019; Polito & Stevenson, 2019). Micro-doses are classified as sub-perceptual or sub-threshold doses. The absence of the classical psychoactive psychedelic effects does not mean a lack of total effects and users have self-reported various benefits ranging from mood enhancement, increased attention and energy to improved creative thinking and the relief of problematic mental health symptoms associated with depression, OCD, ADHD, PTSD, narcolepsy, migraines, and pain (Kuypers et al., 2019; Ona & Bouso, 2020; Polito & Stevenson, 2019).

Microdosing is a common process used in drug development and drug selection in which minute doses of a drug are used to investigate and assess the relative pharmacokinetics (Kuypers et al., 2019; Ona & Bouso, 2020). In the context of psychedelics, microdoses are lower than the general dosing classifications of very-low, low, medium, and high doses used in clinical trials. Psychedelic microdosing schedules also vary, with no as-yet established best practice. The most commonly reported regimen may be to dose once every three or four days (one day on, two days off) in order to avoid cellular tolerance (Polito & Stevenson, 2019; Marschall et al., 2022). It is notable that anecdotal reports of microdosing vary widely, with some users opting for larger ‘microdoses’ that may qualify in a clinical trial as a ‘very low’ dose.

Pre-clinical studies of animal models in this area are limited, and many older studies would not meet current methodological or ethical standards. In a recent study, intermittent low doses of DMT given to rats produced an antidepressant-like phenotype with enhanced fear extinction suggesting that psychedelic microdosing may alleviate symptoms of mood and anxiety disorders in humans (Cameron et al., 2019). One review of both human and animal microdosing trials suggests it may facilitate cognitive as well as emotional enhancement due to beneficial and persisting brain changes, enhancement of neural plasticity and neurogenesis, or reduction of neuroinflammation (Rifkin et al., 2020).

Laboratory studies have documented changes in pain perception, time perception, conscious state, and neurophysiology as a result of low doses of various psychedelics (Polito & Liknaitzky, 2022). Neuroimaging of healthy volunteers who took both a low dose (0.160mg/kg) and high dose (0.215mg/kg) of psilocybin demonstrated both increases and decreases in regional cerebral blood flow in the frontal, parietal, temporal, limbic, cingulate, and occipital cortex, insula, caudate, putamen, pallidum, amygdala, hippocampus, and thalamus (Lewis et al., 2017). Lewis et al. (2017) concluded that psilocybin reduces global cerebral blood flow (gCBF) and produces hyperfrontal effects, even at low doses. Kuypers et al. (2019) suggests that this decrease in gCBF even at lower doses may relate to its psychological effects. They also note that the stimulation of 5-HT_{1A} receptors may be implicated in the reported reductions in anxiety, but also increased mood swings (Kuypers et al., 2019). The downregulation of the 5HT_{2A} receptor may be a mechanism of action for putative therapeutic benefits at lower doses

(Kuypers et al., 2019). Very low doses of psilocybin have also been found to have anti-inflammatory effects (Flanagan & Nichols, 2018; Yu et al., 2008) and may be beneficial to microbiome health and brain-gut communication (Kuypers, 2019). It is plausible that, similar to regular doses, the improvements in mood and reductions in depression symptoms are due to the selective binding by classic psychedelic compounds of 5-HT_{1A}, 2A, 2C receptors and subsequent glutamate release (Halberstadt, 2015; Ona & Bouso, 2020). It is posited that low doses of psychedelics could play a role in treating affective disorders by increasing cognitive flexibility and subsequently decreasing rumination (Kuypers, 2020).

Microdosing effects could be differentially explained by expectancy and/or placebo effects. One systematic study showed that strongly held beliefs in the putative benefits of microdosing psychedelics may influence respondents' interpretations and reporting of microdosing benefits (Polito & Stevenson, 2019). Such expectancy effects may be paradoxical or unlikely, however, as there was no demonstrated evidence of change in expected domains such as creativity, mindfulness, and a sense of well-being. Dosing and frequency of dosing also appear to be unrelated to reported outcomes, indicating that any involvement in microdosing at all, as opposed to dose-dependency or frequency, has explanatory power (Polito & Stevenson, 2019). Concerns around expectancy bias may be overstated (Polito & Liknaitzky, 2022). There is little evidence for enduring effects of microdosing once an individual stops their regimen (Polito & Stevenson, 2019).

Two systematic reviews have been completed on the potential benefits of microdosing (Ona & Bouso, 2020; Polito & Liknaitzky, 2022), in addition to several recent reviews and systematic studies (e.g., Kuypers et al., 2019). Contradictory results have been reported, and there is a clear need for additional dose-controlled empirical research. Underlying mechanisms remain unclear, though as mentioned above, Kuypers (2019) suggests the importance of benefits to the gut microbiome and other possible mechanisms could be related to the psycho-plastogenic effects of psychedelics along with their neuroprotective and neurotrophic-enhancing properties which may, in turn, indicate usefulness in treating Parkinsons, neuroinflammatory or neurodegenerative diseases (Ona & Bouso, 2020), and/or pain (Johnstad, 2018). The most recent and most comprehensive systematic review completed to date identified several lines of evidence indicating direct drug effects in the microdose range, including beneficial changes to cognitive processing and improved mood (Polito & Liknaitzky, 2022).

By 2020, ten observational studies, three qualitative studies, and four randomized double-blind placebo-controlled clinical trials had been published, most frequently investigating psilocybin and LSD (Ona & Bouso, 2020). Reviews of controlled psychedelic microdosing trials report changes in time perception, increased stimulation, distance from ordinary reality, and sense of peace (Kuypers et al., 2019). Also reported are improved mood, energy, and cognition; increases in convergent and divergent thinking; and reduced negativity and increased open-mindedness (Polito & Stevenson, 2019). Increased anxiety and a cyclical pattern of depressive and euphoric mood states were also found (Kuypers, 2020).

Marschall et al. (2022) recently reported a double-blind, placebo-controlled, within-subject crossover study that investigated repeated microdosing effects on self-reported interoceptive

awareness, emotion processing, anxiety, and depression. Exclusion criteria included individuals with substance use disorders and/or currently taking medication, individuals with serious physical or mental health issues, and a personal or family history of schizophrenia, psychosis, mania, and borderline personality disorder. The intervention involved five to seven self-administered microdosing sessions over three weeks, followed by a two-week break, then another five to seven doses over a second three-week period. Out of 75 initial participants, 63 completed baseline measurements, 58 participants completed measures at both S1 and S3, 55 completed measures at both S2 and S4, and 49 completed measures at baseline, S2 and S4. Mood and anxiety symptoms were measured by the DASS-21, emotion processing was measured with the emotion go/no-go task, and interoceptive awareness was measured by Multidimensional Assessment of Interoceptive Awareness Scale (MAIA). Results showed no significant difference in interoceptive awareness, emotion processing, anxiety, or depression from baseline to end of study (two months total). The authors note that the lack of effects on anxiety and depression contradict previous studies that demonstrated reductions in negative emotionality in surveys of people who microdose (e.g., Anderson et al., 2019; Johnstad, 2018; Polito & Stevenson, 2019). This is perhaps explained by study participants' mental wellbeing at baseline, as they used healthy volunteers whose depression and anxiety scores were all within normal range (Marschall et al., 2022). Also, unlike the other studies, Marschall et al. included a placebo condition, used only psilocybin, and had a relatively short microdosing period of three weeks. The authors suggest it is possible that at low doses, it may take longer for serotonergic psychedelics to take effect, similar to the typical two-month delay in measurable effects with conventional serotonergic antidepressants. While Marschall et al. (2022) remain interested in further studies that account for expectancy effects and other placebo responses, they conclude that their results consistently indicate that microdosing has no effect on anxiety and depression. Limitations included selection bias (most had previous psychedelic experience), participants easily broke blind, variability in the psilocybin dose, a large drop-out rate, and the possibility that the study was underpowered due to the small sample size.

Cavanna et al. (2022) published results from a randomized, double-blind, placebo-controlled, within-subjects trial ($n = 34$, 11 females, mean age 31 years) among Spanish-speaking participants in Argentina. Participants were randomized to receive an active dose (0.5g psilocybin mushrooms) or placebo, separated into two weeks with one week between between measurements. In addition to self-report scales and performed tasks and computer-based tasks, the following questionnaires were used: Big Five Inventory (BFI), State-Trait Anxiety Inventory (STAI-T / STAI-S), Short Suggestibility Scale (SSS), Positive and Negative Affect Schedule (PANAS), Mind Wandering Scale (MWQ), Perceived Stress Scale (PSS), Tellegen Absorption Scale (TAS), Psychological Well-being Scale (BIEPS), Flow State Scale (FSS) Creative Personality Scale (CPS), Cognitive-Affective Empathy Test (TECA), and Cognitive Flexibility Scale (CFS). They also conducted a resting state EEG analysis and local-global ERPs and measured physical activity as a proxy to indicate mood and well-being. In addition to measuring changes from baseline to follow-up, this study also assessed preexisting motivations and expectations of the participants. Results demonstrated impaired performance on cognitive tasks after ingesting a psilocybin microdose, and neither the EEG nor ERP analysis of local-global deviants demonstrated a significant effect of the microdose on conscious information

processing. There was no detected effect on physical activity and no significant effect on creativity, cognition, or self-reported measures of mental health and well-being. The authors concluded that although there were significant subjective effects, these were notably inconsistent across participants, and this study did not provide evidence for improvements in mood, creativity, well-being, or cognition, which are typical anecdotal claims made about microdosing (Cavanna et al., 2022). This study was limited by a small sample size, very short duration, focus on acute effects as opposed to cumulative effects over time, and the fact that participants were all healthy volunteers who were already planning to begin a microdosing schedule.

Survey studies have been valuable in understanding the perceived benefits of microdosing. Anderson et al. (2019) identified the most commonly reported benefits: improved mood (26.6%), focus (14.8%), creativity (12.9%), self-efficacy (11.3%), and energy (10.5%) with reported reductions in the consumption of caffeine (44.2%), alcohol (42.3%), cannabis (30.3%), and tobacco (21%). Over 20% of participants in one survey reported microdosing for depression (Lea et al., 2020). A 2020 online survey reported benefits to the improvement of depression (71.8%) and anxiety (56.5%), with improvements in memory (38.8%), attention (59%), and sociability (66.5%) (Cameron et al., 2020). While people who microdose may report an acute boost across a range of psychological variables, the effects do not appear to be sustained over multiple days. Further, longer-term microdosing may be associated with improved mental health and attentional abilities, but also increased neuroticism (Polito & Stevenson, 2019).

Reported adverse experiences of microdosing psychedelics include safety concerns regarding illegality, physiological discomfort, impaired focus, increased anxiety, social interference, cognitive interference, self-interference, and increased symptoms (Anderson et al., 2019). Some users have reported panic attacks, increased anxiety, physical and gastrointestinal discomfort, cramping, restlessness, over-stimulation, insomnia, impulsivity, and reduced cognitive performance (Ona & Bouso, 2020). Clinical trials have reported increased anxiety among study participants who ingested LSD in comparison to those who took placebo or lower LSD microdoses, and studies have reported increased blood pressure and higher frequency of headaches among participants receiving microdoses of LSD (Ona & Bouso, 2020). Kuypers (2020) suggests that increased anxiety may be linked to the emergence of latent emotional content. Other potential adverse effects include the possibility of cardiac valvulopathies due to the repeated agonism of serotonin 5-HT_{2B} receptors (Kuypers et al., 2019).

The psychedelic microdosing literature remains early and exploratory. Clear limitations on existing clinical study designs include lack of randomized placebo-controlled trials, small sample sizes, selection bias, variable potency of doses, and expectancy effects. In addition to a paucity of trials, the existing studies often exclude people with previous adverse psychedelic experiences; further, up to 50% of participants had previous psychedelic experiences, thereby affecting trial bias and external validity (Ona & Bouso, 2020). Another major issue across studies is that some trials allowed participants to smoke tobacco and drink coffee before and after experimental sessions (Ona & Bouso, 2020). The fact that psychedelic studies are highly sensitive to context and setting may also present a challenge in design of clinical trials where the goal is quite explicitly to isolate the effect of the substance itself, as is the case with

microdosing. Placebo-controlled clinical trials in depressed individuals are necessary in order to fully understand the therapeutic effect, how microdosing may have similar or differing outcomes compared to clinical trials at regular doses, and how different compounds may have different effect patterns (Kuypers, 2020). As mentioned, there are also competing definitions of microdosing. Passie (cited in Kuypers et al., 2019) comments that many individuals who “micro-dose” actually take mini doses with some perceptible effects and that the most common dosing regimen may be to simply take one occasional dose without systematic or regular intake. It is also possible that people who microdose in a systematic way also adopt other lifestyle changes (e.g., diet, exercise, meditation) that can help regulate mood and promote a sense of wellness.

Methodological issues that limit the validity of survey studies include variable size or potency of doses, expectancy bias, and differing dosing schedules among respondents. Also significant, differences in microdosing organic *Psilocybe* biomass in contrast to synthetic psilocybin may also affect outcomes and require further study, especially given the presence of other alkaloids and compounds in the whole mushroom, namely baeocystin and norbaeocystin. Additional randomized, placebo, and dose-controlled trials are necessary, as well as additional research into underlying biological mechanisms of action.

The effects of microdosing on sustained attention and vigilance also require further study given the negative effect of these domains on serotonin reuptake inhibitors. Indeed, Cavanna et al.’s (2022) study found impaired performance on cognitive tasks. Further trials should also investigate the role of dopamine activation, identification of underlying mechanisms of action, the role of gut bacteria in microdosing, as well as the long-term effects of chronic microdosing, especially given the potential cardiac impacts of chronic 5-HT_{2B} agonism, which has been previously associated with heart valve fibrosis (Rifkin et al., 2020).

Preliminary findings support the exploration of the safety and therapeutic efficacy of microdosing psychedelics for depression. Polito and Liknaitzky (2022) reviewed eight modern, placebo-controlled laboratory studies specifically focused on the effects of microdosing; six tested multiple doses within the microdose range and all of these studies showed clear dose-dependent changes across a range of measures. Future trials should consider creative blinding mechanisms to reduce expectancy bias, as well as comparative studies between people with psychedelic experiences and those without (Kuypers, 2020). Other recommendations for future research on microdosing include accurate measurement of substance and dose (which may depend on bodyweight), reframing microdosing as supra-perceptual (i.e., may have light to moderate perceptual effects), improved control for placebo response, improved specificity of outcome measures, more representative samples, and more long-term longitudinal studies (Polito & Liknaitzky, 2022). The microdosing discussion may best be served by clarifying doses ranges (microdose, very low dose, low dose) for each psychedelic compound and recognizing the factors known to modulate therapeutic drug effect, including belief, trust in the modality, setting, and the matrix of cultural beliefs (Feeney, 2014).

6.0 Research-Related Considerations

6.1 Safety

Potential adverse reactions and drug interactions in clinical trial settings

The use of psychedelics is associated with adverse experiences such as anxiety, panic or dangerous behaviours (Barrett et al., 2016; Johnson et al., 2008), and in some cases such experiences can lead to ongoing psychological concerns (Carbonaro et al., 2016). Adverse reactions to psychedelic drugs have been classified as ranging from acute/transient and persisting to chronic (Strassman, 1984). Acute or transient adverse effects are described as those which resolve during the acute effects of the drug or soon after the effects wear off (i.e., later that day or that week). Delayed and/or persisting reactions may occur between the two endpoints, such as delayed panic reaction, (more rarely) psychosis, and the observed phenomenon of delayed headaches (Johnson et al., 2008; Johnson et al., 2012; Strassman, 1984). The likelihood of potential adverse effects in clinical trials will be related to dose and the quality of the overall experience and will be modulated by careful screening and evidence-based eligibility requirements (Johnson et al., 2008). Adverse effects related to psychedelics need to be understood not just for their incidence and frequency, but also their duration. Further, some conversation needs to occur which investigates the therapeutic functionality of at least some of the experiences considered adverse since the psychologically challenging nature of certain psychedelic experiences may at least play some role in the putative therapeutic effect (e.g., Gashi et al., 2021). For example, ayahuasca purging is reported as an adverse effect yet is often perceived as a physical, psychological, or even spiritual cleanse by people who experience positive shifts in their experiences following (Fotiou & Gearin, 2019).

Although psychedelics are relatively safe and have a low risk profile for chronic and compulsive patterns of use that characterize addiction, their administration involves psychological experiences which pose unique risks. The most likely risk is distress/anxiety/panic during drug action and usually early in the timeline of drug effect (Johnson et al., 2008; Strassman, 1984). Such psychological states can lead to potentially dangerous behavior. For example, study subjects have attempted to leave study sites or have locked themselves inside a bathroom. Less common are any prolonged psychotic states triggered by psychedelics (Johnson et al., 2008; Strassman, 1984). Psychedelics can have persisting effects which linger for some time after dosing. These include increased suggestibility (Carhart-Harris et al., 2015), affective and ego instability (Nour et al., 2016), changes to health and social behaviours (Teixeira et al., 2022), and changes to worldview (Nayak & Griffiths, 2022). The vulnerability of subjects during and after treatment sessions requires that trials and treatment providers develop rigorous ethical and practice standards (Anderson et al., 2020b).

Clinical and anecdotal observations suggest the possibility that unconscious or repressed psychological material may be recovered under drug effect, though such revelations are contested and may be problematic (Timmermann et al., 2022). Such experiences may be

challenging and may lead to psychological difficulties persisting after drug sessions. The cascade of images, sensations, emotions, and unique perceptions may result in a breakdown in normal means of processing emotion and information, highlighting the importance of adequate preparation and study inclusion criteria (Strassman, 1984). While there are very few case reports of prolonged psychiatric symptoms following psilocybin or mescaline (Krebs & Johansen, 2013), there are too few reports at too small a scale to establish evidence and there is a great need for rigorous investigations into long-term psychiatric wellness among study participants related to their intake of psychedelics.

Psychedelic trial subjects should be in good general health as assessed by detailed medical history, physical examination, 12-lead ECG, blood chemistry profile, hematology, and urine drug screening (Johnson et al., 2008). Medication and drug use histories should be extensive. Concurrent medical exclusions due to drug interactions include patients on medications with perceptual effects such as tricyclic antidepressants, lithium, haloperidol, selective serotonin reuptake inhibitors, antipsychotics, and MAO inhibitors (Johnson et al., 2008; Sellers et al., 2018). However, as previous sections of this report have made clear, several studies have included the use of other psychiatric drugs in addition to psychedelics without adverse reactions. Drug-drug interactions with psychedelics are complex and many risk assessments concern the potential for serotonin toxicity, the pharmacology of which is reviewed by Malcolm and Thomas (2021).

While many investigators such as Rucker et al. (2018) recommend that concomitant psychiatric medications should be withdrawn, allowing sufficient washout time, such protocol has varied depending on the psychedelic being administered (e.g., ketamine vs. LSD) and for the health concern of interest (e.g., MDD, bipolar, wellness in general). Importantly, antagonists of the 5-HT_{2A} receptor (mirtazapine and most antipsychotic drugs) attenuate response to psychedelics and thus may be contraindicated for clinical research, as is benzodiazepine use (Rucker et al., 2018). Investigators are also encouraged to assess the use of over-the-counter dietary supplements and to exclude those taking potentially problematic substances which affect serotonergic function such as 5-hydroxytryptophan supplements and St John's Wort (Johnson et al., 2008). Nayak et al. (2021) recently analyzed reports from three websites (Erowid.org, Shroomery.org, and Reddit.com) concerning the use of mood stabilizers lithium and lamotrigine among people who took psychedelics. They found a higher risk of seizure and of bad trips when psychedelics were combined with lithium, but not with lamotrigine (Nayak et al., 2021).

Pregnant and breast-feeding women or those not practicing effective birth control are generally excluded from psychedelic trials. While such exclusions may be considered medical best practice, they are problematic for understanding safety and efficacy among these populations – particularly people who breastfeed and suffer from post-partum depression (see Jairaj & Rucker, 2022) or other mood disorders. Given the vaso-constrictive and cardiovascular effects of psilocybin, it has been suggested that potential subjects with uncontrolled hypertension should also be excluded (Johnson et al., 2008; Rucker et al., 2018). Rucker et al. (2018) suggest that medical screening should exclude those with serious neurological, renal, liver, or cardiac disease and all participants should be registered with a local general or family practitioner with consent given to the sharing of their records. Of course, the latter does not

account for diverse socioeconomic populations and those who might not have access to regular healthcare or a general practitioner.

Considerations for exclusion criteria, documenting and mitigating adverse events (AEs)

Treatment of the transient anxiety and distress common to psychedelic trials is generally a matter of reassuring and comforting the patient. A quiet, comfortable room which is aesthetically pleasing and with a minimum of distractions should be available (Griffiths et al., 2016; Johnson et al., 2008). Patients should not be left alone; the common clinical standard for current research is to have two practitioners present throughout the session, typically one of each gender but never both of the opposing gender. Most individuals can be "talked down" with reassurance or gentle touch and a reminder that the experience is drug-induced and time-limited, and that the overall experience is safe (Strassman, 1984). For more severe agitation, rescue medications such as diazepam or other short-acting benzodiazepines should be available, in oral or parenteral form, and given under the supervision of a psychiatrist (Johnson et al., 2008). Major tranquilizers should be reserved for only those rare possible exceptions of severely agitated patients (Strassman, 1984). If rescue medications are used, it may be necessary to arrange an overnight stay and monitoring in the hospital or clinical research facility. Otherwise, participants can leave the research facility accompanied by a friend or relative once the clinical team is satisfied (Rucker et al., 2018).

Based on available data, the incidence of adverse reactions to psychedelic drugs in contemporary research settings is low when subjects are carefully screened and prepared, supervised, followed up, and given moderate-to-high doses of pharmaceutical-grade psychedelics (Johnson et al., 2008; Strassman, 1984). Eight recent double-blind, placebo-controlled studies of psilocybin in healthy volunteers, with follow-up between eight and 16 months, reported "no subsequent drug abuse, persisting perception disorders, prolonged psychosis or other long-term impairment of functioning" (Johansen & Krebs, 2015). Two other recent clinical trials of psilocybin in 54 healthy volunteers found no evidence of lasting adverse effects (Krebs & Johansen, 2013). No serious adverse events have been reported in recent RCTs with psilocybin, demonstrating that psychedelics can be administered safely in medical contexts (Carhart-Harris et al., 2021; Griffiths et al., 2008; Griffiths et al., 2016; Johansen & Krebs, 2015; Johnson et al., 2008; Ross et al., 2016; Sellers et al., 2018; Studerus et al., 2011).

Manufacturers demonstrate safety, efficacy, and quality of investigational drugs with clinical trials. Evaluating the risk profile of the proposed treatment involves safety analyses which identify untoward medical occurrences after exposure to the investigational drug (Allen et al., 2018). Such endpoints, known as 'adverse events' or 'adverse effects' are assessed on an individual basis and also by aggregating data across trials to establish likelihood of adverse drug reactions (ADRs), those AEs which have a reasonable possibility of occurring (Allen et al., 2018).

Identifying, monitoring, and reporting AEs may be more complex and time consuming than the processes involved in establishing the potential benefits; further, considerable variation still

occurs in how trials collect and report on their AEs (Allen et al., 2013; Schulz et al., 2010). A recent Cochrane review established that more specific questioning of study participants leads to more AEs being reported, when compared to more open-ended general methods of enquiry. Severe AEs tend to be well reported by initial open enquiry, while less bothersome or clinically relevant AEs are only reported with subsequent, specific questioning. Best practice seems to suggest that open interviews, in addition to structured ratings, elicit the most comprehensive reporting of AEs (Allen et al., 2018).

A recent mixed-methods systematic review of adverse experiences in psychedelic clinical trials found AEs to be inconsistently defined and often inadequately assessed (Breeksma et al., 2022). This review of 44 articles capturing the trial experiences of 598 trial subjects found treatments to be well-tolerated with few serious AEs. The sole exception was a serious AE related to MDMA administration which involved premature ventricular contractions that required brief hospitalization of a trial subject. Breeksma et al. (2022) conclude that AEs are often poorly defined and probably underreported. No other AEs in this review required medical intervention. Among the authors recommendations were that studies should describe timing and severity of effects more extensively (using scales such as the Challenging Experiences Questionnaire), greater transparency in reporting AEs, consistency in defining AEs, recognition of the potential therapeutic value in AEs, and the need for improved documentation of the full spectrum of unpleasant and harmful but potential transformative treatment-related events (Breeksma et al., 2022).

Trials that have excluded volunteers with a current or a recent personal history of substance dependence, major depression or psychosis, current OCD, dysthymic disorder, panic disorder, dissociative disorder, anorexia nervosa, or bulimia nervosa may have unrealistically low AEs compared to what could occur in real-world situations (i.e., not in the context of a controlled clinical trial) (Johnson et al., 2008). Family histories of psychotic disorders, bipolar disorder, OCD, or other serious mental health conditions have also been common exclusion criteria as have been personal or family history of certain personality disorders such as avoidance and narcissism. Individuals considered genetically susceptible (i.e., with a family history of severe psychiatric disease) are generally advised to abstain from the use of psychedelics. It is suggested that among patients who experience schizophrenia, the consumption of psilocybin mushrooms may induce an acute psychotic state that necessitates hospitalization (Amsterdam et al., 2011).

In addition to the aforementioned conditions, Rucker et al. (2018) suggested exclusion criteria include personal history of repeated violence towards others, recent personal history of suicide attempt serious enough to require hospitalization, and current alcohol or other drug dependence, unless this is the target for intervention. Some investigators have excluded individuals scoring high on the personality traits of rigidity and emotional lability, as these traits are significantly associated with negative experiences under psychedelics (Johnson et al., 2008). Exclusion criteria should be applied judiciously but contextualized to individual trials. For example, trials specific to depression would not exclude those with a depressive diagnosis but may exclude those who require urgent care. Similarly, trials focusing on alleviating end-of-life

distress may allow for the inclusion of those with mild co-morbid disorders (Johnson et al., 2008).

The long-term safety information on classic and atypical psychedelics is generally lacking and merits further study. At this time psilocybin may present the greatest overall safety profile for use in clinical trials. Ketamine is somewhat alone among psychedelics in presenting a risk of problematic use, however there have been no reported incidences of repeated use after participation in a clinical trial. While ayahuasca is often a challenging experience, longitudinal and retrospective surveys of ceremonial use have indicated general safety, especially when led by an experienced guide. In the following sub-sections, we present an overview of the safety considerations for certain substances for which we were able to find more robust information.

Goldberg et al. (2020) conducted a systematic review of psychological outcomes in the post-acute phase (≥ 24 hours) after administration of psilocybin, LSD, or ayahuasca in both clinical and non-clinical (i.e. healthy) samples. Studies involving MDMA, ketamine, iboga/ibogaine, DMT, and 5-MeO-DMT were not included; neither were naturalistic studies or studies that did not report at least one psychological outcome. Since this review is limited to a small group of classic psychedelics (LSD, ayahuasca, psilocybin), it does not provide comprehensive data on the state of clinical trials that investigate all classic and atypical psychedelics. Nevertheless, the results yield good insight into the major issues that merit attention for future trial design.

34 studies were included in the review, half of which used single-group pre-post designs (50.0%), while 16.7% were within-group RCTs and 33.3% were between-group RCTs. The majority of these studies investigated psilocybin (58.3%), 25% investigated ayahuasca, and 16.7% investigated LSD (Goldberg et al., 2020). Most studies (54.2%) included a follow-up assessment occurring on average at 5.54 weeks post-treatment. On average, the final follow-up occurred at 53.34 weeks post-treatment. In general, retention at post-treatment was high (94.5%) as was retention at final follow-up (85.6%). Sample sizes were generally small, with an average of 22.9 participants (range = 6 to 85), 51.5% of which were female, with a mean age of 42.13 years old. Among the studies that reported race/ ethnicity (37.5% of studies), 74.6% participants identified as non-Hispanic white or Caucasian. Studies in this review were conducted in the USA (45.8%), Europe (41.7%), and Brazil (12.5%). Approximately half of the studies (45.8%) included participants with clinical conditions, depression being most common ($k = 4$).

Single-group designs often lacked randomization and measures such as effective blinding that could increase confidence. Risk of bias varied across domains, with blinding of participants and study personnel as well as blinding of outcome assessments being the most significant risk factors for bias. Two potential sources of correctable bias are attrition and selective reporting. Selective reporting bias was commonly rated as unclear, in part due to difficulty in assessing whether the reported outcomes were planned (Goldberg et al., 2020).

There was evidence of funnel plot asymmetry (publication bias) in eight trials. No studies in the sample used an intention-to-treat analysis, which would help address attrition bias. Goldberg et al. (2020) note that selective reporting can be reduced through standardized pre-registration of study hypotheses and publication of hypotheses in Open Science platforms. While some trials

were registered on clinicaltrials.gov, many were not, which Goldberg et al. (2020) suggest increased the risk for opportunistic bias and selective reporting. Indeed, trials often lacked published *a priori* hypotheses. Pre-registration of study hypotheses and data analysis frameworks would help reduce selective reporting bias and increase confidence in this body of literature (Goldberg et al., 2020).

Adverse effects were available for 79.2% of studies, and several studies (29.2%) also included measures of longer-term and persisting adverse effects. None of the studies reported a serious adverse event or persistent adverse effects. The most commonly reported transient adverse effects included headache, anxiety, nausea, and increased blood pressure. Goldberg et al. (2020) found no evidence in their review that psychedelics increased risk for long-term persisting serious negative effects. However, they also note that many of the studies in the review were with healthy volunteers and/or excluded individuals with a personal or family history of psychiatric conditions. They suggest that case reports, population-based surveys, and naturalistic studies can yield more robust information on the potential for serious adverse events or persisting adverse effects.

Considerations for serotonergic psychedelics in general

Serotonergic psychedelics possess relatively low physiological toxicity and have not been shown to lead to neurological deficits, organ damage, or to cause genetic damage or birth defects (Gable, 2004; Johnson et al., 2008; Strassman, 1984). Psychedelics have a low potential for addiction and have not been found to lead to compulsive drug seeking, physical or psychological dependence (Amsterdam et al., 2011; Carbonaro et al., 2016; Johansen & Krebs, 2015; Krebs & Johansen, 2013; Rucker et al., 2016, 2018). Animals do not reliably self-administer psychedelics, likely explained by the fact that euphoria is not a consistent feature of the psychedelic experience, tolerance develops quickly and completely, and there is no known withdrawal syndrome (Fantegrossi et al., 2004). Further, unlike many other psychoactive substances (including legal drugs, prescription medications, and controlled substances), psychedelics do not act on dopamine reward pathways in a manner that seems to correlate with addiction, with the exception of ketamine.

Psychedelics moderately increase pupil dilation, heart rate, both systolic and diastolic blood pressure, and may result in transient hypertension, tachyarrhythmias, and hyperthermia. Other physiological effects which may be considered adverse include: dizziness, weakness, impaired perception, impaired proprioception, tremors, nausea, drowsiness, paresthesia, blurred vision, dilated pupils, and increased tendon reflexes (Johnson et al., 2008; Sellers et al., 2018). Psychedelics affect time perception, synchronization and tapping tempo, and working memory which impairs driving and operation of machinery (Amsterdam et al., 2011). Other commonly reported subjective effects include visual and auditory hallucinations, synesthesia, interactions with entities/persons not physically present, past life experiences and experiences of *jamais vu* (Carbonaro et al., 2016). Some known biological effects of psychedelics such as increased corticotrophin, beta-endorphin, prolactin, cortisol, and growth hormone may have implications for clinical efficacy or safety after repeated dosing (Sellers et al., 2018). Due to the non-selective

agonism of the 5HT_{2B} receptor, chronic microdosing may lead to ventricle heart disease, as a result of cardiac valvulopathies and valvular hyperplasia (Kuypers et al., 2019).

Psychedelics are not regarded as promoting aggression or violence, dangerous behavior or suicide, and accidental death under the influence of psychedelics is extremely rare (Johansen & Krebs, 2015; Krebs & Johansen, 2013; Strassman, 1984). However, psychedelics can produce acute and (sometimes) persisting adverse psychological reactions (Johnson et al., 2008; Strassman, 1984). Case reports that documented acute adverse effects of psilocybin in non-research settings reported short-term psychological distress and fear, individuals putting themselves at risk for harm, and persisting negative psychological or psychiatric problems (Carbonaro et al., 2016). Emergency room and poison control data also confirm that psilocybin ingestion is associated with seeking medical treatment. However, the incidence of psilocybin toxicity is extremely low relative to other substances used non-medically (Amsterdam et al., 2011; Carbonaro et al., 2016; Gable, 2004).

Most published case reports of acute lethal toxicity due to psychedelics indicate the presence of other inebriants, most commonly alcohol (Gable, 2004). Studies which calculate safety ratios between various substances consistently demonstrate several hallucinogens as having the least direct physiological toxicity (Gable, 2004). The oral lethal dose (LD-50) value of psilocybin in rats is 280 mg/kg, thus it is assumed that the equivalent of 17 kg of fresh mushrooms' worth of psilocybin (at average potency) would need to be consumed by a human for a 50% chance of overdose (Amsterdam et al., 2011). Interactions which potentiate toxicity include alcohol and tobacco via their metabolic effect on monoamine oxidase (MAO) inhibiting enzymes (Amsterdam et al., 2011). Animals receiving doses of psilocybin exhibit dose-dependent irregularities in heart and breathing rate as well as mydriasis, piloerection, hyperglycemia, and hypertonia (Kuypers et al., 2019).

Psychedelics and challenging experiences

While their physiological safety is relatively well-established, adverse psychological reactions do occur, in part due to the demonstrated sensitivity of psychedelics to set and setting (Hartogsohn, 2017; Rucker et al., 2018; Strassman, 1984). Psychedelics often cause periods of confusion, disorientation, anxiety, fear, panic, dysphoria, paranoia, and emotional turmoil during the immediate drug effects. In the development of the Challenging Experience Questionnaire, Barrett et al. (2016) identified seven dimensions of difficult experiences (i.e., 'bad trips'): fear, grief, death, insanity, isolation, physical distress, and paranoia. Such adverse effects can last for a few days but there is little long-term research on persisting adverse effects (Johnson et al., 2008; Krebs & Johansen, 2012; Strassman, 1984). The most likely risk associated with psychedelics is the fabled 'bad trip'. Distressing effects may be experienced somatically, sensorially, by the evocation of repressed psychological materials and memories, and at spiritual and metaphysical levels (Johnson et al., 2008). In a qualitative study of 50 Norwegian users of psychedelics who reported having bad experiences (42 men, 8 women), Gashi et al. (2021) found that consistent key features of 'bad trips' were the feeling of losing oneself, going insane, ego dissolution, or ego death. Other experiences included panic attacks, confusion, disturbing visions, and paranoia. Significantly, Gashi et al. (2021) used a narrative theory

approach to understand the nature of these experiences and found that in most cases, the ‘bad’ or challenging experience was interpreted to provide a useful lesson in the individual’s life, or that it was the result of irresponsible or naïve use. This accords with the results of several studies in which ego dissolution/peak mystical experience is associated with a stronger therapeutic effect. While a process of meaning-making could be integral to reframing a ‘bad trip’ as a therapeutic or meaningful experience, there is need for larger-scale studies on how often this occurs, what context is necessary or sufficient for this process, and how likely a ‘bad trip’ will become meaningful among inexperienced or completely naïve users who do not belong to a so-called psychedelic drug culture. There is also a need to investigate whether there are differential perceptions of what causes a ‘bad trip’ among diverse demographics, particularly over-policed communities and marginalized or racialized peoples. In this vein, it is worth investigating whether or not more negative or challenging experiences from naturalistic use over the past 40 years can be in some ways attributed to the generally negative portrayals of psychedelics and their risks in public discourse.

In one survey of challenging psilocybin experiences (Carbonaro et al., 2016), 39% of respondents rated it as among the five most challenging experiences of their lives. Experiences of fear and paranoid delusions may lead to erratic and potentially dangerous behaviours, including aggression towards self or others (Strassman, 1984). Although very rare, in hazardous and unsupervised conditions, individuals under the influence of psychedelics have ended their lives by such acts as jumping from buildings (Gable, 2004; Johnson et al., 2008; Strassman, 1984). Larger doses, taking larger doses than usual, and concurrent alcohol and/or cannabis use are associated with negative experiences in naturalistic or non-clinical settings (Carbonaro et al., 2016).

Younger people may also be more susceptible to adverse reactions (Strassman, 1984). Many psychedelic users report some brief visual abnormalities occurring after acute pharmacological effects wear off, but for only a small minority of users are these effects troubling or impairing enough to be considered clinically significant or warrant the diagnosis of Hallucinogen Persisting Perception Disorder, or HPPD, (Johnson et al., 2008). HPPD is characterized by the re-experiencing of some perceptual distortions associated with drug effects, which may manifest as brief ‘flashbacks’ (HPPD I) or as chronic occurrences over months or years (HPPD II) (Halpern et al., 2016). The symptoms of HPPD range extensively and although this condition is defined in the DSM-V, it is poorly understood, rarely reported, and is most often diagnosed in individuals with pre-existing mental health disorders (Martinotti et al., 2018). Further, HPPD diagnosis is not specific to psychedelics, but include other psychoactives such as dextromethorphan, muscimol, and *Datura stramonium* (Martinotti et al., 2018). The empirical validity of the HPPD diagnosis itself has been questioned (Johansen & Krebs, 2015; Krebs & Johansen, 2012). Halpern and Pope (2003) noted that the wide variety of methodology and definitions in publications on HPPD, as well as the lack of reporting on polydrug use or other medical/psychiatric conditions, creates too many limitations for drawing firm conclusions on the prevalence, etiology, and validity of HPPD diagnosis. HPPD phenomena seem to be associated with polydrug use, pre-existing psychiatric morbidities (Amsterdam et al., 2011), and other somatic symptom disorders (Johansen & Krebs, 2015; Krebs & Johansen, 2012), thus it is considered to be a risk for a ‘distinctly vulnerable subpopulation’ (Halpern et al., 2016).

Population surveys, well-being, and safety

Limited population-level surveys indicate that psychedelics have not been found to decrease mental health. Indeed, as the previous sections have suggested, the use of psychedelics may in fact be a protective factor associated with better mental health status (Johansen & Krebs, 2015). In a US survey on National Drug Use and Health from years 2001 to 2004, 21,967 respondents reported lifetime psychedelic use (Krebs & Johansen, 2013). Lifetime use of psilocybin or mescaline and past year LSD use were found to be associated with lower rates of serious psychological distress (Krebs & Johansen, 2013). Lifetime psilocybin use was also significantly associated with lower rates of inpatient mental health treatment and psychiatric medication prescription, lower rates of panic attacks, and lower rates of agoraphobia. No significant association was found between lifetime psychedelic use and greater risk of any negative mental health outcomes. No relation was found between lifetime use of psychedelics and any undesirable past year mental health outcomes, including serious psychological distress, mental health treatment or symptoms of panic disorder, major depressive episode, mania, social phobia, generalized anxiety disorder, agoraphobia, post-traumatic stress disorder, or non-affective psychosis. There were some associations between use of any psychedelic or use of specific psychedelics and lower rate of mental health problems (Johansen & Krebs, 2015; Krebs & Johansen, 2012). There is a need for updated large-scale surveys on experiences with psychedelics, particularly in light of the potential increase in use over the past few years as psychedelics become more accepted in the mainstream. Further, new surveys should capture other popularly used psychedelics that have not appeared in other general surveys, such as DMT, 5-MeO-DMT, and ayahuasca, as well as atypical psychedelics such as ketamine, MDMA, and iboga/ibogaine, and perhaps *salvia divinorum*, which is not included in this report.

Révész et al. (2021) surveyed 2,974 individuals who are English, Portuguese, and Spanish speakers in a recent cross-sectional analysis of associations between lifetime psychedelic use and psychometric measures during COVID-19-related confinement. Respondents were on average 36 years old, 70% female, 497 regular users of psychedelic drugs, 606 occasional users, and 1,968 non-users. Regular users of psychedelic drugs reported less psychological distress, less peritraumatic stress, and experiencing more social support. The confinement, social isolation, and ongoing stress associated with the COVID-19 global pandemic resulted in remarkable signs of psychological distress. Psychedelic drug use was associated with better health outcomes and lower levels of stress, suggesting that the use of psychedelic drugs might be a protective factor, or that people with better psychometric characteristics are more likely to use psychedelic drugs. Given the self-report nature of the survey, the gender bias in respondents, and factors other than psychedelic drug use, there are several confounding issues which could have influenced reported outcomes. Further prospective longitudinal research is needed to better understand the relationship between mental health status during COVID-19 pandemic lockdowns and psychedelic use, and to better understand the health impacts of non-clinical or naturalistic psychedelic use, especially with respect to the role of social networks and social supports.

Therapist abuse and patient safety in psychedelic-assisted therapy and within clinical trials

There have been multiple documented incidences of abuse within psychedelic therapies, and documentation of abuse within a MAPS-funded clinical trial in Canada. Abuse includes sexual abuse and unwanted contact. Multiple instances of physical and sexual abuse in the context of MDMA therapy have been documented in the period 1977-1985, and such abuse led to the development of the therapeutic “dyad” (two therapists, one male and one female²²) to limit patient vulnerability (Passie, 2018). More recently, multiple instances of abuse have been communicated by various media sources and by patient-survivors²³, including in Canada²⁴ and in the context of ayahuasca ceremonies²⁵. Given the vulnerability of the psychedelic state experienced by patients, and the complexity of consent during and after treatments, the possibility of abuse, and measures to prevent it, must be considered within the risk profile of psychedelic therapies. A MAPS-funded MDMA trial in Toronto was recently shut down by Health Canada over concerns for patient safety. Concerns with the project include failure to follow approved protocol, concerns over quality control and staff training, and a lack of informed written consent from participants.²⁶

Considerations for safety of psilocybin

A pooled analysis of acute, short- and long-term subjective effects of psilocybin across eight double-blind placebo-controlled experimental studies conducted between 1999 and 2008 analyzed data from 110 healthy subjects who had received 1–4 oral doses of psilocybin (Studerus et al., 2011). Most subjects described their experience as pleasurable and enriching. Acute adverse drug experiences included strong dysphoria and/or anxiety and panic but occurred only in the two highest dose conditions and only in a small proportion of subjects. All acute adverse events were managed by interpersonal support, and none required urgent pharmacological intervention. Further, follow-up questionnaires indicated no subsequent non-medical drug use, persisting perceptual disorders, psychosis, or other long-term impairments. However, 12% of subjects did report having experienced negative changes in psychological well-being and/or mental functioning after psilocybin. No incidents of prolonged psychotic reactions or precipitations of schizophrenia-spectrum disorders were found in the 110 subjects studied.

²² We recognize the limitation of a binary gendered approach and encourage more gender-diverse or nonbinary frameworks in thinking about therapeutic dyads.

²³ <https://qz.com/1809184/psychedelic-therapy-has-a-sexual-abuse-problem-3/>

²⁴ <https://www.cbc.ca/news/canada/british-columbia/bc-sexual-abuse-psychedelic-therapy-1.5953480>

²⁵ <https://chacrana.net/community/ayahuasca-community-guide-for-the-awareness-of-sexual-abuse/>

²⁶ <https://www.cbc.ca/news/canada/british-columbia/health-canada-mdma-trial-suspended-safety-issues-1.6520960>

High emotional excitability, younger age, and being confined to a brain-scan machine were the variables most associated with unpleasant or anxious reactions. Low baseline emotional excitability, high scores on the ability to experience absorption, and having had few recent emotional problems were all associated with having a pleasant mystical-type experience. 22% of subjects in the high-dose condition met or exceeded the criteria for deep mystical or transcendent experiences (Studerus et al., 2011).

Data release by COMPASS Pathways from the ongoing U.K. phase IIb trial of psilocybin-assisted therapy²⁷ (25mg, 10mg, and 1mg psilocybin doses) for treatment-resistant depression indicates most treatment-emergent adverse events (TEAEs) have been mild/moderate and resolved within one to two days. 27 of the TEAEs included suicidal ideation, suicidal behaviour, and intentional self-injury occurred across 17 patients and show a dose-response relation, with more TEAEs reported among higher-dose groups. 14 of the TEAEs were reported as treatment-emergent serious adverse effects (TESAEs), with 10 of these 14 TESAEs occurring more than one week after psilocybin. All suicidal behaviours occurred at least one month after psilocybin treatment and were present only in non-responders. Psilocybin was generally well-tolerated, with no concerns related to vital signs, ECG or clinical laboratory data. The majority of TEAEs occurred on the day of psilocybin treatment and 77.4% resolved on the same day or the day after. Most of these events were mild or moderate in nature and included headache, nausea, fatigue. TEAEs involving hallucination and illusion started and resolved on the day of administration. These data may reflect the nature of treatment-resistant depression, given high rates of suicidal ideation within this treatment group.

While there is inconsistency in reporting AEs across psilocybin trials, the Anderson trial for demoralization among long-term AIDS survivors reported 511 TEAEs across the 12-week trial (Anderson et al., 2020a). 217 TAEAs occurred in the 25mg psilocybin arm and were reported by 96.7% of participants, 203 occurred in the 10mg arm (96.7% of respondents), and 91 in the placebo arm (reported by 89.7% of respondents). 67% of all TEAEs occurred and resolved on the day of psilocybin administration and most frequent TEAEs were visual hallucinations, illusions, headaches and altered mood. No serious TEAEs were reported and no AEs led to removal from the study.

Considerations for MDMA in particular

Sessa et al. (2019) note that MDMA provides a more gentle and easily tolerated state compared to LSD, and is more clinically manageable due to its shorter duration and tendency to enhance feelings of bonding and empathy. All recent controlled clinical trials with MDMA-assisted therapy have reported that the treatment was well-tolerated with no drug-related serious adverse events or adverse neurocognitive effects (Vizeli & Liechti, 2017; Sessa et al., 2019). In the popular media and drug war propaganda, there has been a conflation between clinical MDMA use and

²⁷ <https://ir.compasspathways.com/news-releases/news-release-details/compass-pathways-announces-further-positive-results/>

street use of what is colloquially known as ‘ecstasy’. Recreational ecstasy use may vary in ingredients and adulterants and is also often consumed in the context of polydrug use, thus complicating its safety profile. In the North American context, it is widely observed that MDMA/ecstasy bought and sold on the street (i.e., outside of clinical contexts) are more likely than not to contain adulterants, some of which are benign and others life-threatening. In clinical trials and MDMA-assisted therapy, MDMA has proven safe and tolerable as well as effective in reducing symptoms of treatment-resistant depression, PTSD, and somewhat of alcohol use disorder (Mitchell et al., 2021; Mithoefer et al., 2018; Mithoefer et al., 2019; Sessa et al., 2021). Common side effects reported during peak effects of MDMA include increased blood pressure, increased heart rate, increased body temperature, jaw tightness and involuntary teeth grinding (bruxism), reduced appetite, while post-drug effects might include low mood, irritability, and fatigue (Sessa et al., 2019). Low mood, however, is less common in clinical settings and with follow-up support from a trained practitioner (Sessa et al., 2019).

Considerations for ayahuasca in particular

Ayahuasca presents a unique opportunity to observe a population-level safety profile at a scale greater than psilocybin, LSD, MDMA, and other classic or atypical psychedelics due to its widespread use in international syncretic churches (e.g., UDV, Santo Daime) and the research supported by these institutions. While experts call for more research, the weight of the evidence suggests that occasional or long-term use of ayahuasca within well-structured ritual contexts carries little health risk and, importantly, no addictive potential (Bouso et al., 2012; Fábregas et al., 2010; Grob et al., 1996; Riba et al., 2001). That being said, there are risks and safety issues to be carefully considered. Callaway and Grob (1998) gave an early warning about the potentially dangerous interactions that ayahuasca may have with pharmaceutical medications. They hypothesized that the interaction between the potent monoamine oxidase-inhibiting harmala alkaloids in ayahuasca and the selective serotonin reuptake inhibitor (SSRI) class of antidepressants may induce a serotonin syndrome with potentially grave outcomes. They advised caution when combining ayahuasca with certain pharmaceutical drugs, however there is a need for pre-clinical and clinical studies to fully understand the risk profile of this interaction (see Malcolm & Thomas, 2021). In the context of syncretic Brazilian ayahuasca churches, it is anecdotally known that people who regularly take SSRIs are also long-term participants in bi-monthly ceremonies without adverse reactions, suggesting that there may be a lower risk of serotonin toxicity than generally believed. Research on risks of serotonin toxicity with ayahuasca must account for dose and frequency; for example, in a typical ayahuasca retreat participants may drink high doses several times in a week. In comparison, the context of Brazilian ayahuasca churches are typically characterized by more moderate doses and less frequent ceremonies (e.g., twice a month), as well as a highly standardized recipe that involves only ayahuasca and chacruna. In non-church settings, the ayahuasca brew may contain other plants in addition to *B. caapi* and *P. viridis*, depending on the context of use, and also highly varies in the way the tea is prepared (i.e., the ratio of *B. caapi* to *P. viridis*).

Hamill et al. (2019) offer a recent comprehensive overview of safety and adverse reactions to ayahuasca and concur on the low risk of dependence, non-medical use, and tolerance. Fairly immediate adverse effects commonly related to ayahuasca use are nausea, vomiting, and

diarrhea (e.g., dos Santos, 2013; Riba et al., 2003). The work of Gable (2004) is often cited when emphasizing the low risk of severe psychiatric consequences. He concluded that ayahuasca is not a trigger for sustained psychosis based on the rates of psychotic episodes among members of the UDV, one of the Brazilian syncretic churches that use ayahuasca on a regular basis and potentially over many years. Other studies of long-term users in the Brazilian religious context also report no negative indications for personality, cognitive deficit, or psychiatric symptomatology (Barbosa et al., 2012; Bouso et al., 2012; dos Santos, 2013).

While Hamill et al. (2019) note in some detail the various physiologic effects of ayahuasca on the endocrine and immune system, as well as pupil size and body temperature, the research does not point to any conclusive sustained negative impacts. Heart rate and diastolic blood pressure are cited to temporarily increase in a dose-dependent manner and although cardiac events are possible there is no evidence for a direct causal association with a single or sustained dosage. Using an animal (rat) model, Pic-Taylor et al. (2015) investigated the toxicity of ayahuasca and determined that the lethal dose is higher than 50 times a typical dose used in a syncretic religious setting in Brazil. There have been no deaths directly attributable to ayahuasca use, although deaths have occurred in non-medically supervised shamanic retreat settings. With respect to use during pregnancy, dos Santos (2010) concluded that while some animal studies show toxicity from *in utero* ayahuasca use, no serious adverse effects of human *in utero* exposure have been documented, although the authors also note that more research is needed before safety is fully understood.

In sum, acute administration of ayahuasca leads to some unpleasant immediate effects such as nausea or diarrhea, moderate increases in blood pressure, heart rate, and body temperature, as well as impact on various indices associated with the endocrine and immune system. However, these effects are temporary, and acute administration in a controlled environment to healthy individuals presents good tolerability. While more research is needed to establish clear guidelines, most experts agree that contraindications for ayahuasca use include the use of serotonergic drugs/medications, as well as previous cardiac and hepatic pathologies (dos Santos, 2010).

Rocha et al. (2022) present a list of recommendations for the management of psychological adverse reactions in ayahuasca trials, which include: effective pre-screening, providing an environment which is calm and with limited external stimuli such as lights and sound, verbal reassurance, calm attention to patient needs, risk minimization (such as assisting subjects when they need to use the bathroom), ensuring that drug effect is resolved and the subject is stable prior to release, and the provision of follow-up after treatment sessions. Widely accepted protocols for ayahuasca include screening for contraindications such as those with previous psychotic symptoms, as well as ensuring proximal and well-integrated therapeutic supports. Such protocols build upon guidelines for psychedelic-assisted therapy from the earlier generation of research and clinical applications (Hoffer, 1970).

Ketamine

A systematic review conducted by Short et al. (2018) analyzed 60 studies for side effects associated with ketamine administration (both single and repeated doses) among patients with depression. In the studies analyzed, psychiatric, psychotomimetic, cardiovascular, neurological, and other side effects were more frequently reported after ketamine treatment than placebo. The most common psychiatric side effect was anxiety. Other commonly reported psychiatric side effects were agitation, euphoria, delusions, panic, apathy, detachment, emotional blunting, psychosis, emotional lability, craving attention, and formal thought disorder. One study included in the review had a suicide attempt by a participant (Singh et al., 2016). Ketamine-related psychotomimetic side effects include dissociative symptoms, derealization, depersonalization, and hallucinations, which may be unpleasant or may resemble a psychotic state, depending on the severity of symptoms (Acevedo-Díaz et al., 2020). The most common psychotomimetic side effect found by Short et al. (2018) was dissociation, while other commonly reported side effects included perceptual disturbance, odd sensations, and feeling 'strange.' 72% of studies that administered IV ketamine reported psychotomimetic side-effects, as compared to 36% of studies that used non-IV administration methods. Increased blood pressure and heart rate were the most commonly reported acute cardiovascular side effects. Palpitations, chest pain, tightness, dizziness on standing, decreased blood pressure, and decreased heart rate were also noted in some studies. However, these effects typically were resolved within 90 minutes of ketamine administration. Headache and dizziness were commonly reported neurological side effects. Less common neurological side effects included sedation, drowsiness, faintness, light-headedness, poor coordination, tremor, and involuntary movements (Short et al., 2018).

Cognitive side effects found in the Short et al. (2018) review included poor memory, poor concentration, confusion, and cognitive impairment. 53% of the studies included reported various other gastrointestinal, ocular, respiratory, and urological side effects. The most common of these was blurred vision and nausea, while insomnia, decreased energy, fatigue, restlessness, dry mouth, vomiting, and crying were also commonly reported. The authors noted that most side effects were associated with IV ketamine administration as opposed to other modes of administration. Of significance, most side effects were reported to occur immediately after receiving a single dose and were resolved shortly after receiving the dose. Additionally, Yoon et al. (2019) found that reported side effects seem to reduce remarkably or diminish with continual ketamine administration, indicating increasing tolerability with continuous dosing. Acevedo-Díaz et al. (2020) conducted a meta-analysis of secondary measures drawn from five substudies conducted at the US National Institutes of Health involving a single IV dose of ketamine for depression. While the Short et al. (2018) study draws on passive monitoring, Acevedo-Díaz et al. (2020) conducted the first active and structured surveillance of emerging side effects (SEs) by study personnel after ketamine administration, inquiring comprehensively into both dissociative and non-dissociative SEs. Similar to other reports, they found that SEs were largely transient and resolved within four hours post-infusion (Acevedo-Díaz et al., 2020). No serious, long-lasting SEs were associated with a single infusion of 0.5mg/kg of ketamine, neither was there evidence for increased recreational use or addiction during the three-month follow-up.

Individuals with hypertension or cardiac instability (such as arrhythmias, congestive heart failure, angina, coronary heart disease, etc.) should likely avoid ketamine due to the hemodynamic changes that occur following administration (Schüttler & Schwilden, 2008). Ketamine has been shown to increase heart rate, heart contractility, and oxygen demand (Graf et al., 1995). While this increase is benign in most healthy individuals, it may pose life-threatening consequences for individuals with pre-existing conditions. Additionally, individuals with thyroid conditions should avoid ketamine as they may already have an increased heart rate, and ketamine has the potential for inducing tachycardia or hypertension in these individuals (Schüttler & Schwilden, 2008).

Although our review indicates that ketamine has potential in the treatment of substance use disorders, it has been suggested by other authors that individuals with an active substance use problem should avoid ketamine, as they may have an unpredictable reaction to consuming multiple drugs (Schüttler & Schwilden, 2008), and may become addicted to ketamine itself. However, this report by Schüttler and Schwilden (2008) concerns anesthetic use of ketamine and not sub-anesthetic therapeutic use under controlled psychotherapeutic settings. This suggestion also contradicts the promising outcomes of several studies we have reviewed concerning ketamine for opioid use disorders, cocaine use disorder, and alcohol use disorder. Schüttler and Schwilden (2008) propose that ketamine should not be used in individuals in an active manic phase of bipolar disorder as it may worsen their worrisome state and potentially activate psychoses. For the same reasons, Schüttler and Schwilden (2008) suggest that individuals with active delusions, hallucinations, schizophrenia, or any form of confusion or delirium should also avoid ketamine. Nevertheless, as reviewed in section 4.2.3, ketamine has been trialed for treatment-resistant bipolar disorder with promising results and no serious adverse events reported.

Individuals with abnormal or decreased liver function should avoid ketamine as it is metabolized primarily by the liver. Both isomers of ketamine are hepatically bio-transformed by cytochrome P450s (Dinis-Oliveira, 2017). Thus, administration in an individual with altered levels of CYP450 may result in unfavourable blood levels of ketamine and its metabolic products. Similarly, individuals with alcohol use disorder or current alcohol intoxication should avoid ketamine. In the case of a clinical trial of ketamine-assisted therapy for alcohol use disorder, extreme caution should be taken.

Schüttler and Schwilden (2008) report on the pharmacokinetics of ketamine use in anesthesia and while we use their findings here for a broad explanation, it is important to keep in mind that our report concerns a range of sub-anesthetic doses that likely differ in the extent of their physiological and subjective effects. Further, many of the trials we have discussed involve a psychotherapeutic component, which is obviously not part of anesthetic use of ketamine. Racemic ketamine has been shown to relax the tracheal smooth muscle (Schüttler & Schwilden, 2008) and also to decrease the bronchial smooth muscle constriction induced by the vasoconstrictor endothelin 1 (Sato et al., 1997). Ketamine antagonizes the vagal nerve to reduce bronchoconstriction and therefore ketamine should be avoided for individuals with decreased lung function (Brown & Wagner, 1999). Gregers et al. (2020) conducted a systematic review on the use of ketamine as an anesthetic for traumatic brain injury (TBI) to investigate the

risk for increased intracranial pressure and reduce cerebral perfusion. Results from 11 studies revealed inconclusive evidence for the effect of ketamine in traumatic brain injury, with two studies showing a small increase and two a small decrease in intracranial pressure (Gregers et al., 2020). Despite some reports of slightly elevated intracranial pressure, there was no evidence of harm associated with anesthetic ketamine use in TBI care.

Ketamine is ranked as a 'category B' substance for pregnancy, meaning that animal studies have not yet demonstrated a risk to the fetus and there are no adequate well-controlled studies in pregnant women to understand the full effects (Schüttler & Schwilden, 2008). Thus, ketamine should be used with caution in this population. Lastly, individuals with a prior bad reaction to ketamine or whose healthcare providers have advised them otherwise should avoid consuming ketamine.

Ibogaine

Information related to the safety profile of ibogaine has been summarized by Brown (2013), emphasizing at the outset that there is no evidence to suggest that ibogaine leads to chronic compulsive use in humans (or animals), nor prone to lead to anything resembling addiction, in large part because of its aversive side effects such as ataxia and nausea and the often-challenging subjective experience. However, evidence from both preclinical studies and clinical reports signal significant health risks associated with ibogaine use. Such risks occur at least in cases in which ibogaine is used to treat substance use disorders when there are pre-existing medical comorbidities (such as poor cardiac health or a history of myocardial infarction); with dosages beyond what is generally accepted among experienced practitioners; or when opioids or cocaine are used in close temporal proximity to ingestion of ibogaine (Mash, 2018). These authors also note that the risk of bradycardia (i.e., significant slowing of the heart rate) is also commonly reported.

Using ibogaine to treat substance use disorders, in particular to assist in withdrawal from opioids, has been widely practiced for years in an underground sub-culture of clinics and practitioners (Alper et al., 2008). Researchers have, however, gathered considerable information about the experiences of participants, including risks and adverse consequences. The most serious of the complications with a possible causal link to ibogaine is the risk of sudden death. Alper and colleagues (Alper et al., 2008; Alper et al., 2012) documented that there were at least 19 cases since 1990 whereby individuals have died suddenly within 76 hours of ingesting ibogaine. The death of a 24-year-old woman shortly after her treatment with ibogaine for detoxification from heroin in the Netherlands in 1993 reportedly led to the cessation of treatments in that country by NDA International and dampened Dutch enthusiasm for the further investigation of ibogaine as a medicine (Alper et al., 2001). It is also said to have dampened NIDA's enthusiasm for supporting clinical trials for the treatment of substance use disorders with ibogaine (Alper, 2001). No conclusive cause of death was determined and although preliminary evidence suggested the possibility of concomitant opiate use this was not confirmed by any post-mortem analysis.

Given these concerns related to sudden deaths, and their impact on policy and regulation, an analysis was undertaken of all available autopsy, toxicological, and investigative reports, in addition to interviews with treatment providers and other firsthand observers, to assess the possible role of ibogaine in each of the 19 deaths (Alper et al., 2012). The authors determined that, in 12 of the 14 cases for which there was adequate post-mortem data, a pre-existing medical condition (usually cardiac) or the concurrent use of other drugs (usually opiates or cocaine) in addition to ibogaine adequately explained or contributed to the sudden death. It was determined that there was no clinical or post-mortem evidence indicating a characteristic syndrome of neurotoxicity. Cardiac disease was a contributing factor or proximate cause in six of the deaths, indicating the importance of heart problems as a risk factor in sudden deaths following the ingestion of ibogaine.

Experts in this area generally agree that patients in the ibogaine medical subculture are at significant risk due to lack of clinical and pharmaceutical standards, as well as the absence of regulations pertaining to the manufacture and storage of ibogaine (Brown, 2013; Mash, 2018). Deaths are reported to have declined as underground practitioners in clinical settings have become increasingly aware of the risks to patients and of practices for minimizing such risk. Precautions include pre-treatment EKG and liver function tests, medical and psychiatric exclusionary criteria, and the presence of physicians or trained emergency medical technicians (Brown, 2013). Interest remains high in the potential role ibogaine might play in the treatment of substance use disorder, based in large part on well-documented clinical case reports (Cloutier-Gill et al., 2016), the ongoing work to establish safe dosage levels for treatment (Schep et al., 2016), and its suggested efficacy for opioid withdrawal from two recent observational studies (Brown & Alper, 2018; Noller et al., 2018). Considering the current opioid crisis in Canada and the US, there have been recent calls for more concerted research into the role that ibogaine might play in responding to this crisis as an additional treatment option (Argento et al., 2019a; Mash, 2018).

6.2 Research Design Issues

6.2.1 Clinical Trial Design

Research suggests that nonpharmacological variables are responsible for a major part of therapeutic benefits in a variety of accepted drug treatments beyond psychedelics (Hartogsohn, 2017). In addition to set and setting, the psychological supports provided in clinical psychedelic research studies contribute to therapeutic outcomes, thus limiting our knowledge of the pharmacological effects on their own (Rucker et al., 2018; Sellers et al., 2018). For example, recent RCTs with psilocybin for distress related to life threatening illness have shown significant effect sizes, yet these studies provided extensive psychological support and gains were often noted even prior to psilocybin administration (Rucker et al., 2018; Sellers et al., 2018; Sellers & Leiderman, 2018). Challenges to blinding creates expectancy effects for both researchers and subjects, potentially biasing outcome measurements and inflating effect sizes. The most significant methodological challenges in psychedelic clinical trial design are the risk of

unblinding and placebo effects, prevalent expectation bias, and the choice of the adequate comparator dose (Mertens et al., 2022).

While an extensive literature exists cataloging a multitude of naturally occurring plant-based and newly synthesized chemicals, most psychedelic research in humans has been conducted only on small, relatively homogenous sample populations and principally use synthetic derivatives such as psilocybin (Sellers et al., 2018). Further, trial methodology has been often descriptive, open-labelled, and uncontrolled (e.g., phase 1 and phase 2 of regulatory drug approval processes) (Rucker et al., 2018; Sellers & Leiderman, 2018). As discussed, there are significant challenges in blinding both participants and researchers, as well as delineating the drug effects from the psychotherapeutic interventions (Johnson et al., 2008; Rucker et al., 2018; Sellers et al., 2018). Researchers have attributed the relative lack of rigour in the human studies to the national and international regulatory restrictions on possession of and research with psychedelic compounds (Sellers et al., 2018). Due to regulatory controls, special licenses are required to process and administer Schedule I drugs in human trials, driving up research costs and limiting access. Strict security, control, and monitoring protocols are necessary, requiring dedicated infrastructure (Rucker et al., 2018). For these reasons and others, the minimal effective dose, maximum tolerated doses, and optimal dosage of psilocybin and other psychedelics remain unproven (Sellers et al., 2018).

Regulatory drug approval is generally a gradual process that typically begins with early investigative, open-label, and uncontrolled trials to establish safety and tolerability (Phase 1). Phase 2 trials add more methodological rigour and slightly larger sample sizes to establish preliminary indications of therapeutic efficacy. Efficacy is more definitively established, along with indications of effectiveness in Phase 3 trials, which tend to be larger, multi-site RCTs, ideally with more diverse patient populations. Given the profound and obvious behavioural effects of psychedelics and the imperative of blinded, unbiased, and unconfounded trials for regulatory drug approval processes, (Schulz et al., 2010), RCTs with psychedelics face significant challenges.

In planning future trials and charting the course for regulatory drug approval, there exist three major categories of heightened focus: treatment-resistant depression, end-of-life distress/palliative care, and PTSD. The most prescient initial focus may be unipolar depressive disorder, with treatment-resistant depression as a priority. Unipolar depression is rising in prevalence, is often chronic and unremitting, is associated with high risk of suicide, and carries a high socio-economic burden with poorer outcomes than a wide variety of physical health problems (Rucker et al., 2018). Treatment resistance – defined as failure to respond to at least two antidepressants – presents an additional imperative to seek unconventional treatment options. Early trials have established safety, tolerability, and initial indications of efficacy. In addition to the study recently published at Johns Hopkins University (Davis et al., 2021), a large-scale Phase 3 trial is now enrolling in the United Kingdom (Rucker et al., 2018).

While depression may be a larger market with greater financial incentives, regulatory approval for the use of psychedelics in end-of-life distress and palliative care may be an easier process. Safety data requirements may not be as strict when life expectancy is limited and there may be

considerable popular support (Rucker et al., 2018). The largest and most robust clinical psilocybin trials have focused on anxiety and depression resulting from life-threatening illness (Griffiths et al., 2016; Ross et al., 2016). In Canada, Section 56 exemptions to the Controlled Drugs and Substances Act to use *Psilocybe* mushrooms were granted to four terminal cancer patients in 2020 for psilocybin-assisted therapy in end of life care, stimulating further national interest in pathways for compassionate access to psychedelic therapies^{28,29}.

MDMA-assisted therapy for PTSD is well into Phase 3 clinical trials, including research locations in Canada, with promising initial results. These trial results validate the MAPS-manualized therapy protocol for moderate-to-severe PTSD, but further trials are needed with differing populations and protocols, especially given the cost implications of such extensive psychotherapy in conjunction with the trial medication.

Although TRD, PTSD, and end-of-life distress stand out as three conditions in which most research resources have been invested so far, it is evident that psychedelic-assisted therapies have high potential in the treatment of addictions/problematic substance use. Ayahuasca, psilocybin, and ibogaine in particular have demonstrated preliminary safety and efficacy in observational and clinical studies. Given the public health emergency of illicit drug toxicity and poisonings/overdoses in Canada and the USA, as well as the high rates and destructive effects of alcohol and tobacco dependence, it is important to ensure that sufficient resources be directed toward well-designed clinical trials of psychedelic-assisted therapy for addiction recovery.

Blinding, placebo, and delineating therapeutic effects

Determining the relative contribution of the psychedelic drug to its putative therapeutic effect is difficult, given the sensitivity to context and the apparent benefits of ancillary psychological supports. However, it would be unethical to give psychedelics without at least a moderate degree of preparation, psychological counselling, and emotional support (Rucker et al., 2018). Further, preparation and integration sessions are considered a ‘best practices’ approach for harm reduction and benefit maximization (Callon et al., 2021; Gorman et al., 2021; see also Timmermann et al. 2022 for discussion on ethical concerns in the therapeutic encounter). It has been suggested that carefully designed RCTs could examine how different contexts and supports interact with psychedelics (Rucker et al., 2018).

Muthukumaraswamy et al. (2021) suggest that trials might be confounded by de-blinding and high levels of response expectancy. In addition to a concern for over-estimated treatment effect sizes due to these confounders, the authors also strongly caution that current psychedelic RCTs generally do not report pre-trial expectancy or the success of blinding procedures. Uthaug et al.’s (2021b) blinded, placebo-controlled naturalistic study of ceremonially ingested ayahuasca

²⁸ <https://www.cbc.ca/news/canada/british-columbia/magic-mushrooms-therapy-1.5675637>

²⁹ <https://www.cbc.ca/news/canada/london/some-doctors-therapists-get-health-canada-permission-to-use-magic-mushrooms-1.5834485>

does discuss the blinding process and post-trial guesses by participants. However, this investigation of the effects of setting and other non-pharmacological factors in ayahuasca ceremonies suffered from methodological issues that make it impossible to draw practical conclusions.

To adequately address the distinctive complexities of placebo-controlled trials with psychedelics, Mertens et al. (2022) make proposals based on a review of methodological inadequacies that have riddled the literature thus far. First, they suggest that an active placebo condition – for example, an active but subtle psychoactive such as niacin/nicotinamide, methylphenidate, or a 1-5mg microdose of psilocybin – is required in studies of psychedelics in addition to active comparators that demonstrate assay sensitivity. An active placebo is necessary in order to limit unblinding in psychedelic trials, especially where a moderate or high dose is expected (Mertens et al., 2022). Second, they address the potential nocebo effects in comparator arms, arguing that there is an ethical imperative to offer every patient a high dose of the psychedelic treatment after assessment of the primary endpoint, especially in trials with participants suffering from major depression and/or have titrated down their psychiatric medications in preparation for the study.

In an inventive study specifically on the placebo effect, Olson et al. (2020) tested non-pharmacological factors in psychedelic use by giving a placebo to college students who expected to ingest a psychedelic substance. This article is exemplary in its description of the study setting and blinding procedures, as well as important observations concerning the phenomena of placebo effects and ‘contact highs’. Results found strong alterations in consciousness with considerable individual variation in responses as measured by the 5D-ASC ($M_{pre} = 1.25 [0.62, 2.08]$; $M_{post} = 3.77 [2.33, 5.54]$). While some participants reported very low or no effects, which drives down average values, others reported effects in line with moderate or high doses of psilocybin and LSD. Such results reinforce the relevance of expectation and context in psychedelic experiences, particularly for microdosing (Olson et al., 2020). The authors suggest a balanced placebo design for future microdosing trials.

In a comment on the review by Muthukumaraswamy et al. (2021), Schenberg (2021) rightly points out that while suggested blinding practices are considered essential for rigorous study of pharmacological effects, isolating drug effects from other variables (e.g, therapeutic alliance & placebo effects) is not reflective of real-world conditions in which “clinical practice patients always expect something out of the treatments they search for”, and therefore these elements are “always part of the process” (p.1317). Such issues put into question the RCT as the ‘gold standard’ in psychedelic clinical research. Indeed, Oram (2014) discusses how the early wave of psychedelic researchers in the 1960s had already called into question the imposition of RCT designs for what was obviously an insurmountable blinding problem. Further, earlier researchers argued that set and setting were elements that should be harnessed in study designs to maximize therapeutic benefit, not ‘controlled’ in the interest of pharmacological reductionism (Oram, 2014). To provide practical conclusions and generalizable results, Jiménez-Garrido et al. (2020) argue that rigorously designed naturalistic studies are a valuable tool for generating data that reflects the context and complex variables involved in ritualistic and other communalistic settings.

Psychedelic trial publications should at minimum provide a detailed description of the set and setting conditions of the trial, including reference to variables such as criteria for subject selection, researcher expectations, subject expectations, preparation activities, and physical setting characteristics. Aday et al. (2022) suggest that investigators take measures to reduce participant expectancy in the design of the study via recruitment and selection methods, incomplete disclosure of the study design, use of an active placebo, and measures of participant expectancy and blinding efficacy. In addition, variables such as gender, racial or ethnic identity, and age are valuable factors to consider in terms of set, setting, and expectancies. This will allow for separate trials to be compared and contrasted, facilitating a more nuanced understanding of how the various aspects of set and setting function and interact in research settings (Hartogsohn, 2017). Good clinical practices form the basis for well-controlled studies, characterized by the ability to clearly distinguish drug effects from factors such as placebo effect or observation bias. (Sellers et al., 2018).

In contrast to early hospital-based LSD research, contemporary settings for psilocybin research have been less clinical and more comfortable for the participant experience. Generally, modern experiments have taken place in comfortably furnished rooms with sofas, pillows, and aesthetically pleasing features. Subjects were encouraged to relax, recline, and listen to curated music through headphones. The social setting was non-threatening, staffed only by trained personnel with whom the subject had developed a trusting relationship in which a framework for preparation and integration of the experience is communicated. Contemporary studies with such settings have far fewer adverse events than earlier studies. Given the sensitivity to context demonstrated for psychedelics, an aesthetically pleasing environment is thought to decrease the probability of acute psychological distress. Researchers often create a living room-like setting, with comfortable furniture, and a non-clinical aesthetic with the ability to control temperature, lighting, and colours (Johnson et al., 2008; Strassman, 1984). The environment should be designed to accommodate any potential perceptual changes and disorientation. The setting should be locked and secure, with no potentially dangerous objects. Windows should be double or triple paned, and locked. The session room should not have a telephone or any extraneous or invasive sounds. There should be easy access to a private, unlockable bathroom (Johnson et al., 2008; Sellers et al., 2018; Strassman, 1984).

General summary of clinical trial design, demographics, and strategies for analysis

Large-scale, multi-site, and placebo controlled RCTs are needed to clarify the empirical evidence for specific clinical conditions such as depression, as well as for more experimental trials on healthy volunteers. Selection bias, expectancy bias, reporting bias, active placebo, unblinding, and factors related to set and setting must be thoroughly considered and reported by study authors. Creative study designs are necessary to determine how extrapharmacological and pharmacological mechanisms of action interact without reducing explanations to general 'placebo effects.' Further, it is recommended that future trials consider the transdiagnostic potential of psychedelics when planning hypotheses and outcome measurements (Kočarová et al., 2021; Gorman et al., 2021). There is a well-known and highly problematic lack of diversity in study participants, which must be addressed to increase generalizability (Williams & Labate,

2020). Important factors for increasing diversity of clinical study populations include creative recruitment processes, plans for ensuring study retention, and community education efforts. There is also a lack of gender and racial/ethnic diversity in study therapists and in scientific leadership positions (e.g., principal investigators, lab directors, clinical supervisors) that has implications for outcomes in clinical trials as well as real-world applications (Michaels et al., 2018). For further discussion of equity and diversity, see section 6.2.3.

The results of this review indicate several considerations for clinical trial design and analysis. First, the registration of clinical trials in forums such as clinicaltrials.gov, Open Science Framework, or [AsPredicted.org](https://aspredicted.org) will facilitate searches by researchers (such as the one done for this current report) as well as reduce opportunities for selective reporting. Related, the publication of *a priori* hypotheses, when possible, will also reduce opportunistic bias. Attrition bias can be mitigated through reporting an intent-to-treat analysis and full reporting on the participant drop-out rate. To date, selection bias is tricky to address since it can be difficult to recruit participants who do not have a pre-existing interest in the use of psychedelics, particularly in light of recently shifting representations about psychedelics and their therapeutic potential in mainstream and social media. However, more analytic attention and clear reporting on potential selection bias and participant demographics (e.g., racial or ethnic identity) will contribute to more transparency. As previously mentioned, there is a need for creative recruitment strategies to ensure the participation of underrepresented populations. Examples of recruitment strategies for hard-to-reach populations include: respondent-driven sampling, Indigenous field worker sampling, facility-based sampling, targeted sampling, time-location sampling, and cluster sampling (Shaghghi et al., 2011). Swanson and Ward (1995) provide a list of barriers to participation in clinical trials as well as methods and strategies for recruiting minority populations, which include some of the following: developing deep and sustained relationships with communities and community leaders; recruiting clinical investigators from minority populations, providing small grants to minority clinics, and/or establishing a clinic or study site in the community; develop educational materials for community members and for clinicians/health professionals part of that community; offer to cover travel costs, participant time, childcare, free meals, and other relevant costs; use interviewers and study coordinators that are known in the community; and ensure that consent forms and recruitment material are clearly translated and easy to understand.

6.2.2 The Importance of Mixed Methods and Naturalistic Design

Naturalistic observational studies contribute essential information to the overall body of knowledge regarding the therapeutic potential of psychedelic substances and various integrated treatment protocols. These studies can triangulate findings from clinical research to (1) go beyond treatment efficacy to treatment effectiveness in real-world settings; (2) suggest new hypotheses, topics, and sub-populations of interest; (3) indicate aspects of set and setting and treatment content for further exploration in controlled trials; and (4) raise cautionary flags concerning safety and risk factors. These advantages counterbalance the various limitations of naturalistic/observational work, namely, selection bias in cross-sectional survey work or studies

of people participating in ceremonial retreats, expectancy bias without blinding, and other features of uncontrolled research designs.

Research on ayahuasca and other plant-based entheogens such as peyote, iboga, and psilocybin mushrooms intersects with a growing interest in and international support for traditional medicine in general³⁰ (World Health Organization, 2000). Ayahuasca is particularly well-situated on the bridge between ancestral medical traditions and the modern, westernized medical application of psychedelics, given its widespread and normalized use as a therapeutic agent among Indigenous and mestizo communities in the Amazon basin, and its rapid global spread for religious and healing purposes, as well as high interest among researchers (Labate & Cavner, 2011; Labate et al., 2014; Tupper, 2008). In both ancestral and modern applications, the role of set and setting, also referred to as the therapeutic “context” (Carhart-Harris et al., 2018c), have important relationships to treatment outcomes as well as risk. Since the real-world context of ayahuasca and iboga ingestion often occurs in ritual-ceremonial settings traditionally grounded in a complex cosmology with epistemological frameworks that differ in many ways from the bioscientific perspective, it is necessary to include a creative research design outside of a highly controlled clinical setting.

The role of “context” resonates with developments in the science of program evaluation, in particular realist evaluation and complex interventions (Pawson & Tilley, 1997; Rog, 2012), summarized succinctly by the phrase: “outcome = intervention + context”.

There is much to be learned outside of, and in addition to, clinical trials research, including surveys of naturalistic psychedelic use, outcome measurement, and qualitative observational research conducted in ceremonial, retreat, and informal settings. Clinical trials focused on outcomes are positioned largely for regulatory drug approval, yet other significant domains remain equally relevant for study. For example, patient experience, community-based research, and observational research are needed to help better understand the total social impact of psychedelics and to explore potential clinical or other potential benefits.

Notwithstanding the power of the RCT for causal inference and minimizing bias, there are many criticisms about the research design underpinning such trials and their value for establishing evidence-based health care (e.g., Cohen et al., 2004; Hyde & Delphin-Rittmon, 2014). Some of these challenges may be exacerbated in the study of psychedelic-assisted therapeutics.

Sackett, who many would quite rightfully consider the “grandfather” of research ratings and development of evidence-based guidelines, clearly recommended careful consideration of the appropriate research design for a given research question, the best choice not always being the RCT (Sackett & Wennberg, 1997). In reporting on the application of the WHO GRADE system for mental and substance use disorders, Barbu et al. (2010) highlight several challenges including the lack of attention to important qualitative work and non-experimental studies, two factors they note as being particularly challenging in reviewing evidence relevant for low- to

³⁰ See also: <https://www.who.int/initiatives/who-global-centre-for-traditional-medicine>

middle- income countries where clinical trials have yet to be undertaken for the interventions in question. These authors also note that the evidence-base underlying interventions for mental and substance use disorders also needs to be weighted with information on values, preferences, and feasibility, again being particularly sensitive to the context of low- to middle-income countries. This also applies to generalizing to the most marginalized populations in high-income countries, including Indigenous communities.

A major criticism often levelled at the RCT as the foundation for evidence-based treatment guidelines is the representativeness of the study sample after successive stages of establishing the criteria for study admission, recruitment, consent, and loss to follow-up (Melberg & Humphreys, 2010; Rothwell, 2005). A classic example of recruitment challenges is the usual strategy to exclude people with alcohol or drug problems from the study sample when assessing the efficacy of pharmaceutical agents for depressive or anxiety disorders. This approach flies in the face of evidence that shows the high levels of co-morbidity of these mental health challenges and substance use disorder (Chan et al., 2008). As a result, the findings emanating from the trial are not necessarily generalizable to a significant proportion of people suffering from the targeted mental disorders.

Another major concern with the RCT research paradigm is the challenge with causal inference when evaluating complex interventions (Stame, 2004). The aim of an RCT design is to use a placebo condition and randomized assignment to carefully control, if not remove entirely, the influence of extraneous factors and thereby strengthen the inference about the causal link between the intervention and outcomes. However, in many situations, research outcomes are inextricably linked to the context in which the intervention is delivered thereby rendering the logic of the RCT far from ideal - in fact, not logical at all. This challenge presents itself in many areas of public health and health care (Craig et al., 2008) and is particularly problematic in the use of RCTs in the study of psychedelic-assisted treatment, including those based on a traditional medicine paradigm. Although the RCT continues to be referred to as the 'gold standard' of empirical investigation in health-related clinical studies, it is a contested mode of knowledge production that is often inappropriate for drawing firm conclusions about therapeutic interventions that work on multiple levels (e.g., intra- and inter-personal, contextual, societal). The first recognized clinical trials to use the double-blind RCT design tested the use of Penicillin patulinum among British officers and factory workers afflicted with the common cold (1943-4), followed by a 1948 trial testing streptomycin for pulmonary tuberculosis (Jones & Podosky, 2015). This methodology proved insightful in establishing evidence for pharmaceutical interventions that are relatively mechanistic in nature; however, its extension into behavioral interventions and even surgical interventions has been highly disputed.

The concept of the RCT as the 'gold standard' did not emerge until as recent as 1982 in an attempt to establish broad standardization for evidence-gathering in medicine and while the RCT is a powerful methodological tool, scientists and clinicians recognize that clinical research must draw on flexible standards and a variety of methods in the pursuit of safe and effective therapies (Jones & Podosky, 2015). As noted earlier, the current weight of evidence and expert opinion suggests that contextual factors such as mode of preparation, ritualistic/religious application, background and experience of the healer/facilitator, characteristics of the patient,

including previous use of the medicine in question, and individual and community belief and value systems, to name just a few factors, are likely to play an important role in therapeutic effectiveness (Loizaga-Velder & Verres, 2014; also see commentary by Langlitz, 2012b). In short, a purely experimental research paradigm modelled after western evidence-based medicine and its hierarchy of evidence is not *de facto* the ideal approach for evaluating psychedelic-assisted treatment for mental and substance use disorders given the complex interplay of substance, set, and setting.

Generally speaking, a range of research approaches should be pursued that will include the kinds of designs most likely to support regulatory approvals for routine clinical practice. These should be complemented by other research methods, including naturalistic observational studies, case studies, single subject designs, population-based epidemiological work, and realist synthesis. Regular knowledge synthesis activities are also needed that include not only narrative reviews, rapid reviews, scoping reviews, and systematic reviews, but also the engagement of people with lived and living experience, including family members who bring another perspective to interpretation of what we “know” and where more work is needed in support of their recovery journeys.

6.2.3 Diversity/Equity Representation in Current Research

The so-called renaissance of psychedelic medicine has stimulated a great deal of excitement, yet it also elicits skepticism among those who are hyperaware of the historical patterns of erasure and inequity when it comes to political and technological (i.e., medical) innovations (George et al., 2020). Some authors have taken attention to the question of equity in psychedelic-assisted therapies in the Global North, particularly concerning inclusion of Black, Indigenous, and other people of color (BIPOC) in research populations, in practitioner training programs, in conducting research, in influencing and forming policy, and whether psychedelic-assisted therapies will be culturally informed for non-white or non-affluent communities (Michaels et al., 2018; Thrul & Garcia-Romeu, 2021; Williams et al., 2020). People of color, which include African Americans/people of African descent, Native American/First Nations, Hispanic/Latinx, and Asian-Americans, comprise less than 20% of the clinical study population in research on psychedelics (Michaels et al., 2018). In their meta-analysis of psychedelic-assisted psychotherapy since 1994, Luoma et al. (2020) found that people of color were largely absent from the studies reviewed. There are no studies to date on the extent to which transgender, queer, and people who identify as lesbian, gay, bisexual, or gender nonconforming are included in clinical research (Sevelius, 2019). People who do not identify as heteronormative or gender-conforming may have special considerations for trauma related to family dynamics, social dynamics, and/or sexual abuse. The underrepresentation of diverse populations has implications for generalizability in terms of pharmacology as well as whether or not certain therapeutic modalities are culturally appropriate for different ethnic communities and other subcultures. Challenges to generalizability implicate equity issues concerning whom these novel therapeutic processes are being designed for and who has limited access (financially, culturally, physiologically). For example, most forms of emerging psychedelic-assisted psychotherapy rely on accessibility to a psychotherapist and/or medical doctor for treatment,

which is known to present challenges for people from socially or economically marginalized communities, and for people who particularly seek practitioners who identify as BIPOC and/or LGBTQ2S+.

Further, there are implications for continued systemic neglect of race-based trauma that people of color may suffer due to histories of slavery, attempted genocide, sexual assault, forced schooling, and medical abuse. Community-based research approaches such as Thomas et al.'s (2013) study of ayahuasca for alcohol use disorder among First Nations participants is an important contribution for thinking about culturally appropriate psychedelic-assisted mental health interventions. More qualitative research like this is important both for communities and for the potential to lead to more refined clinical studies and appropriate policy. In North America, Williams et al. (2020) conducted a cross-sectional online survey (n = 313) of naturalistic use of classic psychedelics or MDMA among Black, Indigenous, and other people of color. Although based on self-report, their results suggest that classic psychedelics or MDMA evoked significant reductions in depression, anxiety, and traumatic stress related to experiences of racism. Diverting funding to pursue this kind of research is important for exposing the kinds of mental health conditions that underserved communities struggle with and for determining what kind of research is of primary concern for communities of color.

BIPOC communities need to be part of the conversation and leadership as psychedelic research expands. Racialized stigma is strongly associated with illicit drugs in terms of the origins, evolution and current application of drug control and criminalization of people who use drugs. Additionally, an unfortunate amount early pharmacology and medical research exploited vulnerable communities such as African Americans, First Nations, institutionalized and incarcerated people. Thus, careful steps should be taken to shape an inclusive and equitable research agenda in Canada which eliminates race-based disparities (Michaels et al., 2018; Strauss et al., 2021). Psychedelic-assisted therapies have been proposed as effective means to respond to racialized trauma and chronic exposure to micro-aggressions.

A general limitation in the psychedelic medicine and psychedelic-assisted therapy literature is that published studies and policy recommendations are almost exclusively from the western bioscientific perspective (Tupper & Labate, 2014). Many classic psychedelics such as *Psilocybe* mushrooms, ayahuasca, peyote, huachuma/San Pedro, *bufo* (5-MeO-DMT), yopo, and others were developed and continue to be used in ancestral traditional contexts. Indeed, many non-indigenous people opt to partake in traditional or neo-traditional ceremonies rather than in a secular manner, which attests to the continued importance of such traditions in the therapeutic process for both Indigenous and non-indigenous people. It is important that psychedelic medicine and policy take into consideration the knowledge, wisdom, practices, policies, and traditions of these communities that are often not represented or are underrepresented in Canada. This will contribute to improving equity, potential benefits, and accessibility. It is hoped that taking attention to these communities and traditions will also contribute to their ability to thrive through the perseverance of ritual and ceremony.

Concrete steps toward improving equity in psychedelic research may include the following:

- Invest in research training opportunities for students at all levels (undergraduate, graduate, postdoctoral) who identify as BIPOC, LGBTQ2S, neurodiverse, and/or a person with a disability.
- Ensure funding opportunities for projects conducted by people who identify as BIPOC, LGBTQ2S, and/or as having a disability, or projects that directly serve such communities or populations.
- Sponsor community-driven initiatives that seek to create socioculturally appropriate spaces for education and/or care (e.g., BIPOC community integration groups, disability community integration groups, LGBTQ2S integration groups, conferences or symposia that center people representing such groups or that cultivate inclusive spaces, and community educational opportunities appropriate for specific groups).
- Include voices from marginalized groups in policymaking processes to ensure accessibility.
- Ensure that policies or drug scheduling schemes do not reproduce inequities and oppressions that have tended to characterize drug policy.
- Ensure that new policy related to psychedelic-related medicine/therapy allows for the continuation and innovation of Native/ Indigenous/First Nations communities with respect to ancestral medicines.
- Invest in investigators who engage with Indigenous research methods and/or community-based participatory research.

7.0 Additional Considerations for a Contemporary Canadian Psychedelic Research Agenda

7.1 The Role and Rights of Indigenous People

Considerations of current research gaps and opportunities in the Canadian context is not complete without discussion of issues related to the Indigenous peoples of what is now known as Canada. The authors recognize the complexity of this topic and the need for perspectives and experience beyond our own expertise. We also acknowledge that no one among us (the writing team) self-identifies as belonging to an Indigenous community. Nevertheless, we strongly advocate for the responsibilities of all stakeholders in this area to improve the well-being of Indigenous communities within Canada, especially considering historical evidence of attempted ethnocide and genocide. We also acknowledge that our rapid review itself has been undertaken largely from a non-Indigenous worldview of scientific inquiry (LaFrance et al., 2012; George et al., 2020).

Keeping in mind our study aims to summarize the extant body of knowledge and include expert opinion, we will draw upon several salient papers and key documents to highlight issues that we feel are particularly critical for moving research in this area forward in the Canadian context.

First, it has been established under the 2007 United Nations Declaration on the Rights of Indigenous Peoples (Assembly, 2007) that Indigenous peoples have a human right to maintain their traditional medicines and healing practices. While this declaration does not supersede international law, it significantly advanced recognition of Indigenous rights and gives stakeholders in research and practice related to psychedelic medicine some important principles of good practice. In Canada, this is now being formalized in legal statutes such as British Columbia's 2019 provincial Declaration on the Rights of Indigenous Peoples Act.

Indigenous peoples have used a wide range of psychoactive plants for millennia in a ritualistic context that emphasizes community wellbeing, healing, rites of passage, and spirituality, and which also provided a context for safe usage (Fotiou, 2019; Rochester et al., 2021).

Anthropologists have made the plausible link between the use of these plants to attain an altered state of consciousness and the origins of art and religion (e.g., Furst, 1972).

Unfortunately, the popularization of Indigenous medicines has sometimes had disastrous effects on communities and plant or animal populations. Perhaps the most famous example is the case of psilocybe mushrooms from Mexico, a situation in which 'magic mushrooms' became highly sought after beginning in the 1960s, leading to dramatic changes for the communities of origin due to drug-seeking tourists, spiritual tourists, and enthusiastic researchers and journalists. A similar drama is being played out today in the globalization of ayahuasca and the proliferation of foreign-owned ayahuasca retreat centers in the Amazon. Concerns about plant sustainability and impacts on local communities increase each year. The current crisis in peyote cultivation

and protection is a pressing issue that complicates political projects to legalize all plant-based psychedelics, since Native American communities rely on the current legal structure to deter non-Native use of this sacred plant. Mike Jay (2019) provides an insightful overview of the historical popularity of peyote among non-Indigenous peoples, while Davis (2017) recounts these issues through research and personal experience (see also, IPCI Communication Committee, 2021; and Iron Rope et al., 2020). Minimally, researchers and other stakeholders engaged in the research enterprise need to acknowledge the risks to Indigenous people associated with appropriation of these medicines and to treat their origins with respect.

Indigenous peoples have a different understanding of several key concepts inherent in the dominant Westernized worldview of scientific inquiry (Tuhiwai Smith, 1999; Wilson, 2008). One of the most salient differences is an understanding that all things are living and dynamic, including knowledge. As a knowledge-generating practice, it follows that research projects must be conducted in a way that respects the connections between plants, humans, and non-humans, and which benefits the community as a whole. Another prominent difference is the understanding of healing as a holistic process that cannot be disaggregated in the search for active ingredients of the healing process and discrete mechanisms of action. Related to this is the notion that nothing exists nor can be understood outside of its context. This is lucidly explained by Wilson (2008) who describes Indigenous epistemology as the development of ideas through relationships. This includes the formation of relationships between people as well as relationships between ideas and the contexts from which they emerge. The idea cannot be separated from its context, lest it lose its shape (Wilson, 2008, referring to a concept proposed by Terry Tafoya). Methodologies such as storytelling and analogies reinforce the relationship-building process. To achieve rigorous study from this perspective, methods and practices of meaningful engagement must allow for observation and direct experience with the object of study in its natural context. This in turn pivots the researcher towards experiential learning, storytelling, and the use of analogies to convey meaning. Many of these principles are embedded in Indigenous evaluation frameworks (LaFrance et al., 2012) as well as complexity-based and realist evaluation models (Rog, 2012).

Indigenous people have longstanding traditions, cultural mores, and guidelines concerning who is qualified to serve as a traditional healer or practitioner. These traditions have significant implications for research protocols with many of the psychedelic medicines under investigation. This also has implications for training and certification of future practitioners who aspire to engage in research projects. Importantly, Rochester and colleagues (2021) excluded traditional ritualistic applications from consideration of credentialing in the Canadian context out of respect for the guidelines established by the relevant communities of practice. This bifurcation of Westernized practices of psychedelic-assisted therapy and ritualistic practice begs the question as to whether or how they might be combined to understand their effectiveness, for whom, and under what conditions (see for example, Rush et al., 2021). A culturally-attuned, trauma-informed psychotherapy has been proposed with special consideration for the devastating impact of the legacy of forced assimilation and the discovery of mass graves associated with Indian Residential schools (Avalos, 2021; Muscat et al., 2021). The Muscat et al. (2021) contribution is ground-breaking in its practicality with respect to starting with (currently legal) ketamine-assisted psychotherapy and carefully articulating the principles and processes

required to decolonize this approach through meaningful collaboration and partnership with a cross-cultural integrated approach to understanding both mechanisms of action and articulation of outcomes.

Finally, Indigenous peoples have rights to control research and resulting data that is about them, and which may impact their communities. In Canada these principles are enshrined in OCAP, which stands for Ownership, Control, Access and Possession (<https://fnigc.ca/ocap-training/>). OCAP principles assert that First Nations have control over data collection processes and that they own and control how this information can be used. Researchers engaging with Indigenous people and their communities in the study of psychedelic medicines will need to ensure the OCAP principles are reflected in their research protocols and ethics submission. This includes engagement of Indigenous researchers and others as appropriate to the project goals and objectives such as Elders, other knowledge keepers, and community members.

All of the above, in addition to other key points of intersection, contributes to a special circumstance here in Canada and elsewhere to engage in a dialogue with Indigenous researchers, leaders, key institutions, Elders, and communities. We emphasize the necessity to foreground their perspectives on this emergent field of psychedelic science, especially those aspects with historic links to traditional sacred plants. This dialogue needs to cover some of the key points of divergence identified here, especially with respect to production of knowledge and its purpose. Fotiou (2019) sums up the way forward to decolonize psychedelic science by highlighting the “need for a shift in paradigm, one that will acknowledge the validity of Indigenous worldviews as equal partners to scientific inquiry” (p. 16).

7.2 A Public Health Perspective: Prevention, Health Promotion and Healthy Drug Policy

From a public health perspective, the potential re-scheduling of psychedelics for therapeutic or even non-medical purposes may lead to an increase in their use among the wider community. Indeed, there has been a notable increase over the past few years in advertising, conferences, symposia, and workshops for the general public on both microdosing strategies and practices for larger doses. While there is justifiable concern that a population-level increase in the prevalence of psychedelic drug use might lead to more adverse incidents, it is noteworthy that an analysis of harms associated with various psychoactive substances – ranging from alcohol and tobacco to more stigmatized substances – showed LSD and psilocybin to be ranked among the lowest risk of all those studied (Nutt et al., 2010). The low potential for patterns of chronic and compulsive use of psychedelics is also noteworthy, as are current findings from recent epidemiological studies which indicate improved well-being, likely associated with general anxiolytic and antidepressive effects. It stands to reason that population-level studies among people who use psychedelics should also consider other lifestyle factors that users might engage with either as a result of psychedelic use or independently. While there is some evidence from cross-sectional survey research for an association between psychedelic use and improvements in select substance use disorders, personality disorders, PTSD, and past suicide

attempts (Shalit et al., 2019), these are admittedly correlational and not necessarily causal relationships.

A recent survey among ayahuasca drinkers in the Netherlands (n = 377, 50.1 female, mean age 48.8 years) found that regular participation was not associated with any relevant health harms (Kohek et al., 2022). Participants in the study had better general well-being, fewer chronic or lifestyle-related diseases, more physical activity, and a more balanced diet in comparison to normative Dutch data. Importantly, while this group reported higher use of illegal drugs, there were no reported associated harms. Basedow and Kuitunen-Paul (2022) conducted a systematic review of 37 articles that reported on motivations for use of serotonergic psychedelics, organizing results according to ‘expansive motives’, ‘coping motives’, and ‘enhancement motives’, which were most commonly reported, as well as ‘social’ and conformity motives, which were rarely reported. Their results indicate that most psychedelic users who have been studied are interested in some sort of self-knowledge, healing, or pleasurable pursuit, though further investigation into user motivations at a population level are warranted.

Other studies of psychedelic use in the general population show no relationship to psychosis among those who reported use of classic psychedelics, and also demonstrated enhanced wellbeing, lower needs for formal mental health treatment, and a reduced risk of suicide (Hendricks et al., 2015b; Sexton et al., 2020). The general direction of these findings has also been confirmed in other population-level research (Johansen & Krebs, 2015), including research on marginalized populations with very high risk of suicide (Argento et al., 2017). Further population-level research is needed to fully establish the balance of public good vs risk in increasing access to psychedelics. As discussed in the previous section, such benefit-risk calculations must also account for the well-being of communities in which practice with these substances originated and continue to be important to cultural vitality.

Haden et al. (2016) previously offered a “framework for the regulation and management of psychedelics based on public health principles” (p.7). The re-positioning of psychedelics as compounds of potential clinical, spiritual or other kinds of benefit requires large-scale regulatory reform of current Canadian drug policy. Although seemingly monumental, this reform possibility is not without precedent. The previous medical cannabis regulatory framework provides several important lessons for therapeutic access to psychedelics as decided between a medical practitioner and patient, in addition to allowing for the expansion of further research and ease of restrictions for researchers.

Legal access to cannabis began with section 56(1) exemptions in 1999, followed later by an appellate court ruling affirming the right to possess cannabis for medical purposes (Regina v. Parker, 2000) and the subsequent creation of Marihuana for Medical Purposes Regulations (Government of Canada, 2016). Charter challenges argued that the limits on those regulations contravened constitutionally protected rights, and the Government of Canada legalized cannabis before those challenges were escalated to the Supreme Court. Health Canada can reclassify drugs from prohibition to regulatory approval for medical or other use, and indeed has recently done so. Dronabinol (synthetic delta-9- tetrahydrocannabinol) is one such example, initially approved as an orphan drug for AIDS- related anorexia in 1985 and now approved for

cancer chemotherapy-related nausea and vomiting. Xyrem (sodium g-hydroxybutyrate) was approved for the treatment of cataplexy associated with narcolepsy in 2004, and an extract of cannabis sativa has been licensed for medical application even in regimes of cannabis prohibition (Rucker et al., 2018).

Under Schedule 3 of the Canadian *Controlled Drugs and Substances Act* (CDSA) and Schedule J of the *Food and Drug Regulations*, most psychedelics are illegal to possess, obtain or produce unless authorized for clinical trial or research purposes. There are no current therapeutic products approved for use, though an implicitly tolerated grey-market for commercial distribution of *Psilocybe* mushroom preparations has emerged in Canada with multiple companies selling and distributing both micro- and macro-dose products (Tomoski, 2019).

Authorization for manufacturing or other private work can be requested under the Food and Drug Regulations through a Dealer's License from Health Canada. Numinus, a private firm in British Columbia, has obtained a Dealer's License from Health Canada and is authorized to cultivate *Psilocybe* mushrooms and extract its psychoactive alkaloids. Numinus has recently completed the first flush of legal magic mushrooms production in Canada (Stephen, 2020). Calgary-based PsyGen Labs Inc., Toronto-based PharmAla Biotech, and B.C.'s Filament as well as Numinus are each scheduled to supply domestic researchers with both synthetic and naturally-sourced psychedelics.

Exemptions to the prohibition of controlled substances may be requested under subsection 56(1) of the CDSA, if the Minister of Health believes the exemption is "necessary for a medical or scientific purpose or is otherwise in the public interest" (Government of Canada, 2020). In 2017 Health Canada granted a Section 56 Exemption for the União do Vegetal and Santo Daime to allow serving the sacrament (ayahuasca) (Rochester et al., 2021). As of January 5, 2022, Health Canada amended its Special Access Program to allow medical practitioners to request psychedelics on a case-by-base basis for patients deemed to be in emergency situations. Previously, special exemption could not occur outside the context of a clinical trial or under Section 56 of the CDSA. With the new amendment, a medical practitioner must secure a letter from the Minister of Health to authorize use for the treatment of a serious or life-threatening illness. With this written authorization, the medical practitioner may obtain an unapproved drug from a manufacturer.

Beginning in January 2023, the B.C. government will decriminalize the possession of small amounts of opioids, cocaine, methamphetamine, and MDMA. Multiple jurisdictions in the United States have decriminalized psilocybin mushroom use, including Denver, Oakland, Seattle, Santa Cruz, San Francisco, and Washington, DC (Carpenter, 2020). Further states have voted or are creating legislation to decriminalize use and/or ensure funding for clinical research (for detailed map, see: <https://psilocybinalpha.com/data/psychedelic-laws>). Oregon recently became the first state to legalize access to psilocybin and to lay out a plan to regulate therapeutic use through the provision of psilocybin service centers (Cormier, 2020).

Further research and evaluation are required to compare regulatory and clinical models of psychedelic-assisted therapy, factoring issues of accessibility, cost-effectiveness, and cultural sensitivity. Group ceremonial models have been recently investigated to have positive

outcomes, measured with the construct of acute experiences of *communitas* (Kettner et al., 2021). While clinical trials by design have been premised on individual administration of psychedelics, entheogenic rituals have historically been collective gatherings. Group vs. individual therapy outcomes require further research, especially in light of non-medical social uses. Equity considerations in certification and program models is critical, given the demonstrated under-representation of BIPOC peoples as researchers, facilitators, or study subjects.

In summary, the public health landscape concerning psychedelics is changing with respect to the demographic of users and legal access to substances for both personal and special medical use. It is important to recognize the role of both medicalized and non-medicalized use of psychedelics within the broader scope of drug policy, rather than focus myopically on mental health services and medicine. As Haden et al. (2016) proposed in their vision for regulating psychedelics, a public health model must necessarily be aimed at improving the health of populations through an ethical framework, social justice, human rights, equity, health promotion, harm reduction, and evidence-informed policy and practice. Such an approach recognizes that successful regulation is not complete until anyone who wants access to accurate information and/or high-quality services related to personal or therapeutic psychedelic use are able to achieve this, regardless of socioeconomic status. A public health approach would also be led by officials who have a dedicated expertise in evidence-based drug policy and/or research, and who collaborate with religious and cultural groups to ensure safe and sustainable cultivation or importation of sacred plants (Haden et al., 2016). Given the rising global interest in psychedelics for the treatment of mental health issues, as well as other purposes, it is incumbent upon therapists and public health systems alike to take a harm reduction approach to best serve individuals who are interested in exploring these substances. To this end, Pilecki et al. (2021) propose a Harm Reduction Integration Therapy (HRIT) while Gorman et al. (2021) similarly propose a Psychedelic Harm Reduction and Integration (PHRI) approach for therapeutic practitioners. Also of great significance but beyond the scope of this report for detailed discussion are the ethical and public health implications of the patenting of psychedelic compounds, and in some cases therapeutic procedures, that may limit broader access to high-quality, affordable therapies, and also has implications for biopiracy (Marks & Cohen, 2021; Tupper, 2009). Low risk psychedelic use guidelines, like those that exist for cannabis and for alcohol, would be of benefit in reducing the potential harms of personal use, and monitoring Emergency Department data for presentation with harms related to psychedelics may be of value in health planning.

7.3 Paths to Regulatory Change

Despite the therapeutic promise and growing investment in the field, there are widely acknowledged and significant barriers to scientific and clinical progress. Chief among these is that psychedelics are illegal in most jurisdictions as highly restricted Schedule I substances, thereby making it extremely difficult for the required clinical studies to be approved and funded, and to source and administer the psychedelic compounds at a reasonable cost for research (Belouin & Henningfield, 2018; Marks & Cohen, 2021; Nutt et al., 2013; Rucker, 2015). Barriers

with respect to potential safety and adverse consequences appear to be grounded in the somewhat illogical argument that an evidence-based therapeutic tool of medicine should be banned because it *may be* used for other harmful purposes, an argument that has rarely been invoked in other types of health care including pharmacologic agents, particularly prescription opioids (Dakwar, 2016). It should be noted that so-called harmful purposes often refer to any non-medical/ scientific use or to recreational uses, which are worthy of study in themselves and a focus of political activism as something that people should have a right to in the pursuit of the 'betterment of well people' (Gandy, 2019).

In North America, psilocybin has been decriminalized or legalized in nine US cities and the state of Oregon and is available in Canada through a compassion-based special exemption to the *Controlled Drugs and Substances Act*. Psilocybin, being the most well-studied of the substances reported here, is considered by advocates to have the highest potential for regulatory change such as rescheduling in the near future, though MDMA may also be close to regulatory approval based on clinical trials for TR-PTSD. Several other US states and cities have attempted or currently are attempting legislation for a variety of regulatory changes that include: (1) approval and regulation of psychedelics for medical use (i.e., medicalization pathway), (2) decriminalization of well-studied psychedelics such as psilocybin, (3) reduced penalty statutes for use/possession of certain psychedelics, (4) limited judicial exceptions for certain psychedelics, and (5) directing political or financial resources to establish working groups to study medical use. In the North American context, the medicalization of psilocybin and MDMA has had growing political and financial support in the past decade, spurred by the mounting evidence from clinical trials outlined in this report. Further, an explosive speculative start-up market mostly directed at psilocybin- and ketamine-related services has begun to flourish in anticipation of regulatory changes. Marks (2021) identifies three legal pathways through which substances can be rescheduled in the US context, with a focus on psilocybin: legislative, administrative, and judicial. In the legislative pathway, congress could amend the *Controlled Substances Act* (CSA) to reschedule psilocybin, which may be more realistic than ever in the wake of the Marijuana Opportunity Reinvestment and Expungement Act approved by the House Judiciary Committee (Marks, 2021). In the administrative pathway, the federal attorney general could delegate power to the DEA to reschedule substances. This could occur through an executive order signed by the president or through a petition by the public and government officials to pressure the DEA, though Marks does not consider this a likely possibility. Finally, in the judicial pathway, advocates can sue the DEA after it denies a petition to reschedule psilocybin (or other substances). At this point in time, Marks (2021) considers the judicial pathway to be the most effective, but also suggests that recent political changes will make the legislative pathway more feasible. While legal pathways to regulatory change are increasingly feasible, other stakeholders prefer to avoid the medicalization of psychedelic substances and instead advocate for rescheduling and legislative changes based on religious freedom and/or the right to 'cognitive liberty.' Such stakeholders may support the medical and therapeutic uses of psychedelics in specific contexts but are wary that the medicalization pathway will create a gatekeeping mechanism in which people can only access psychedelics through a health practitioner. People and groups who have structured religious, spiritual, or otherwise non-

medical practices with ayahuasca, peyote/mescaline, psilocybin mushrooms, 5-MeO-DMT/bufo, and other substances must also be afforded legal avenues for use as well.

Public opinion and lack of understanding of the differences in relative risk and potential clinical value between therapeutic protocols and non-therapeutic or recreational use present additional barriers. Related to this is the change in mindset required among the general population, policy makers, clinicians, and researchers alike that non-ordinary states of consciousness may actually be beneficial, especially when integrated into a structured therapeutic framework, as has been done with other therapeutic strategies such as mindfulness and meditation (Dakwar, 2016).

Stigma is also identified as an important barrier going forward, both for patients seeking substance use treatment (e.g., Nielson et al., 2018), as well as for therapists and researchers interested to work in the area. Some of this stigma results from the widely acknowledged and inappropriate condemnation of the use of psychedelics that, in part, led to their inclusion in the *Controlled Substances Act*. Other aspects of stigma arise from clinical sensitivity to treat substance dependence with another psychoactive substance, treatment success with methadone and managed alcohol programs notwithstanding. There is a clear need for improved educational efforts targeted towards clinicians concerning the beneficial and safe uses of psychedelics in light of the misinformed consensus that psychedelic-assisted treatments are a ‘thoroughly discredited’ modality (Norcross et al., 2010). Overall, there is wide variation in stakeholder-specific assessment of the benefit-risk ratio, at both clinical and population levels, and more evidence-based consensus on this equation is no doubt a fundamental requirement for moving the field forward.

In summary, pathways to regulatory change may occur through legal frameworks that rely on strong scientific evidence coupled with public and government advocacy. The catch here is that the current legal framework has presented significant challenges to producing high-quality scientific and clinical studies that would support the rescheduling of substances. Barriers to research include lack of funding for well-designed psychedelic clinical trials, lack of funding for coordinated multi-site randomized trials, and the additional difficulties and requirements in accessing psychedelic compounds for research due to the current regulatory framework in Canada. Further research is also required for understanding the current knowledge, attitudes and behaviors of healthcare practitioners and policymakers pertaining to psychedelics and psychedelic-assisted therapies. Such research reinforces the value of qualitative and ethnographic research methods, for which there is limited funding.

7.4 Training and Certification

In addressing the Canadian context, Rochester et al. (2021) propose the creation of an independent credentialing council to regulate and credential practitioners. Haden et al. (2016) proposed a similar regulatory body – with the suggested name ‘College of Psychedelic Supervisors’ – that would be responsible for oversight of trained and qualified supervisors (e.g., ceremonial leaders, guides, psychedelic therapists, or ‘tripsitters’) who support the use of psychedelics. Rochester et al. (2021) also proposed the adoption of a Code of Ethics among

psychedelic-assisted therapy practitioners, outlining areas of behavior and interaction where participants before, during, and after psychedelic sessions are potentially vulnerable and providing guidelines for healthy boundaries and behavior. Further, the authors propose the development of research-oriented graduate degree programs in Psychedelic Studies, as well as the creation of certificate programs in psychedelic-assisted treatment and integration counseling for mental health practitioners and traditional clergy. Efforts to screen and train therapists, and to develop practice guidelines, codified ethics and professional guidelines are urgently required in Canada in order to ensure patient safety and public trust (Mocanu et al., 2022).

Sanacora et al. (2017) describe a minimally suggested training for clinicians who are administering ketamine. They indicate that clinicians should be licensed and have the ability to administer a Schedule 3 medication. As well, clinicians need to be prepared to cope with cardiovascular risks and have ACLS training. Since people receiving ketamine can experience dissociative effects, clinicians need to be able to manage and potentially treat concerning behaviour. Sanacora et al. (2017) also suggest that clinicians gain expertise prior to independent administration and follow local community standards of practice and/or guidance from clinical practice committees. They suggest that development of standards can be guided by the “Statement on Granting Privileges for Administration of Moderate Sedation to Practitioners Who Are Not Anesthesia Professionals,” published by the American Society of Anesthesiologists.

Phelps (2017) has previously described six core competencies for psychedelic therapists: empathic abiding presence, trust enhancement, knowledge of psychedelic effects, therapist self-awareness and ethical integrity, and proficiency in complementary techniques. While developed for those engaged in psychedelic-assisted therapy, these competencies can extend to other registered health professionals with relevance to psychedelic therapies, including nurses and nurse practitioners, physicians, pharmacists, Registered Massage Therapists, somatic practitioners, mental health counsellors, yoga therapists, and cranio-sacral therapists. Given the historical role of nurses in psychedelic clinical research, there is renewed interest in reviving the previously hidden role of nurses in psychedelic therapies (Denis-Lalonde & EStefan, 2020; Rosa et al., 2019). As mentioned, Gorman et al. (2021) also propose a detailed clinical transtheoretical and transdiagnostic model for Psychedelic Harm Reduction and Integration (PHRI). PHRI emphasizes a harm reduction approach, inquiry, non-directive psychotherapies, and relational-psychodynamic processes.

In addition to the appropriate harm reduction, psychotherapeutic, and basic life support training that have been discussed, the question of whether it is important for the guide themselves to have their own psychedelic experiences has been considered since at least the 1950s (Nielson & Guss, 2018). It is argued that first-hand experience with psychedelics will equip the guide (whether clinician, facilitator, researcher, or ‘trip sitter’) with the necessary insight into these modes of altered states in order to better understand the process of the client, offering heightened ability for empathic connection and interpretation (Earleywine et al., 2022; Nielson & Guss, 2018). In recognizing that client retention and improvement is known to be related to the nature of the therapeutic alliance (e.g., matching on gender, ethnicity, spiritual beliefs, personal values, personal experiences with mental disorder, therapeutic preferences or styles),

Earleywine et al. (2022) conducted a survey (n = 800) of people with depressive symptoms which asked them to rate the importance of a psilocybin-assisted therapy guide who has had their own experience with psilocybin. 22% (177) reported experience with psilocybin and 27% (219) reported experience with hallucinogens. Participants were asked to rate the level of importance (0-100) of their guide's personal experiences on a scale that ranged from 'not at all important' to 'somewhat important' to 'extremely important'. Responses averaged over 63 on the scale from 0-100, which were significantly larger than 'somewhat important', indicating that participants in this survey valued guides who had personal psilocybin experiences. The authors consider personal experience with psilocybin use to be a relevant component of set and setting, particularly in its effect on the relationship between the therapeutic alliance (e.g., shared values and life experiences) and treatment outcomes (Earleywine et al., 2022). Tupper and Labate (2014) discuss self-experimentation among clinicians and researchers, noting that such 'psychosomatic empiricism' has a long history in medical science and suggest the psychedelics (ayahuasca in their particular discussion) offer a role as a 'cognitive tool' or teacher. Nielson and Guss (2018) and Earleywine et al. (2022) observe that the role of personal experience with psychedelics among guides is understudied and undertheorized and warrants significant further discussion and study.

The state of Oregon in the USA is in the process of developing its own model for the regulation of psilocybin use after decriminalizing all drugs (Oregon Measure 110) and authorizing the use of psilocybin-containing products by licensed providers (Oregon Measure 109). This latter measure authorized the development of a program that would allow clients over the age of 21 to purchase, possess, and consume psilocybin at a psilocybin service center or under the supervision of a facilitator after undergoing a preparation session. The Oregon Psilocybin Services (OPS) section of the Oregon Health Authority (OHA) has established a Psilocybin Advisory Board to advise on policies for who is eligible to be licensed as a facilitator, as well as the education, training, and professional code of conduct for facilitators. Importantly, eligibility to become a licensed facilitator requires only a high school diploma or its equivalent and the completion of a training program approved by the OHA. While the Oregon model is but one among many possibilities, this is the first state in the USA and the only known region in the world in which a government-regulated psilocybin program is being developed for general access.

Knowledge translation, practitioner training, and the development of core competencies as well as best practices and practice standards remain high-priority needs if the therapeutic promise of psychedelic-related therapies are to be fully investigated. In addition, there is a need to evaluate different training curricula and processes for professionals who aim to work within a particular scope of practice. Cavarra et al. (2022) conducted a systematic review of psychedelic-assisted therapeutic modalities, finding a broad array of theoretical frameworks and therapeutic preferences. Some leaders in the field firmly advocate for third-wave CBT modalities in psychedelic-assisted therapies (e.g., Sloshower et al., 2020; Watts & Luoma, 2020; Yaden et al., 2022), while others propose more non-directive, relational, transdiagnostic methods (e.g., Brennan & Belser, 2022; Gorman et al., 2021; Pots & Chakhssi, 2022). In developing policy and regulatory frameworks for the training, supervision, and oversight of psychedelic guides and therapists, it is important to remain sensitive to the various stakeholders involved, particularly

traditional practitioners and Indigenous/Native/First Nations groups who have the right to autonomy in spiritual and healing activities.

8.0 Research Gaps and Implications for Funding

This rapid review of the therapeutic application of psychedelics reveals a burgeoning, but uneven and still emergent body of knowledge. MDMA-assisted therapy for PTSD and psilocybin for depression have each been granted “breakthrough therapy” status by the United States FDA; psilocybin is currently in Phase 3 trials, and MDMA for PTSD Phase 3 trials have recently published results indicating effectiveness. Research into psilocybin for end-of-life distress and Substance Use Disorder is similarly moving into more highly powered and rigorous Phase 2/3 trials. Ketamine is the most widely and systematically investigated psychedelic by far (primarily for depressive disorders), but systematic reviews and meta-analyses sometimes find ketamine-associated results to be inconclusive. Early Phase 1 trials of serotonergic psychedelics for migraine or cluster headaches are underway, as are trials for a range of degenerative neurological conditions and traumatic-brain injury. A more widely dispersed and varied body of literature proposes clinical benefit for psychedelics in the treatment of eating disorders and body dysmorphic disorder. Psychedelics are presenting as a novel, emergent and promising treatment for a wide range of clinical and psychiatric conditions, suggesting some shared underlying mechanisms of change which may help identify common or unified bases between apparently separate conditions, that is, transdiagnostic potential.

Given the apparent rapid onset of and persisting anti-depressant effects of ayahuasca and the anti-addiction impact demonstrated in observational studies, more research is indicated for ayahuasca, DMT, and 5-MeO-DMT for depression and for substance use disorder. Given the history of LSD research as a treatment for alcohol use disorder and death-related anxiety, LSD should be researched with contemporary clinical trial design standards, in particular to investigate substance use disorders and end-of-life distress. While no published clinical trials were found investigating mescaline, the health benefits observed among members of the Native American Church indicate the potential for therapeutic application. Ayahuasca, peyote, and huachuma are all culturally significant plants/cactii, requiring protection for Indigenous practices and involvement of Indigenous peoples in research design and implementation. This area is ripe for additional naturalistic study with mixed methods research. Mixed qualitative and quantitative methods should not, however, be restricted only to these naturalistic observational studies but become a standard part of research protocols to help understand the meaning attached to the psychedelic experience and help understand and integrate psychopharmacological, psychological, and spiritual mechanisms of action.

Gaps in research are observed in our synthesis of published trial data and a review of current registered clinical trials indicate a bifurcation of psychedelic research into ketamine and non-ketamine applications, with a disproportionate representation of ketamine trials. Sanacora et al. (2017) noted that more data are needed regarding the efficacy and safety of repeated dosing of ketamine for major depressive disorders. They also note that most studies and case reports to date have only looked at effects of ketamine after less than one month of treatment and encourage more studies to assess the risks of ketamine use over longer time frames. Further,

there is not enough information to know when treatment with ketamine would be considered futile nor what the standard number of treatments should be to optimize benefits over time (Sanacora et al., 2017). Other suggestions for future ketamine research include manipulation of variables (dose, infusion rate, frequency of treatments); evaluating differences based on assigned sex at birth; the effectiveness of ketamine in community-based samples (McIntyre et al., 2020); and developing alternatives to saline as a placebo. Delineating between studies that use ketamine pharmacotherapy only as opposed to ketamine-assisted psychotherapy is highly relevant to interpreting results and to determine how to optimize benefits. Overall, longer term evaluation of participants in future studies is required (Cavenaghi et al., 2021).

The clinical research on classical and atypical psychedelics still requires additional trials to confirm therapeutic dose, optimal number of doses, and the relative contributions of the psychological supports and complementary therapies provided. As clinical research has been predominantly focused on the treatment of individuals, further trials and research are needed into group therapy settings and collective ceremonial rituals, including in naturalistic settings such as ayahuasca ceremonies. Trials comparing the use of natural compounds or naturally extracted compounds to synthetic are also largely missing from the literature. The whole, natural biomass of organic compounds such as psilocybe mushrooms (Kuypers et al., 2019), or the ayahuasca brew (Morales-García et al., 2017) may reveal additional benefits due to an entourage effect as opposed to synthesized psilocybin or DMT. One exception is synthetic 5-MeO-DMT, which is preferable over naturally extracted *bufo* for clinical research since the latter relies on the unsustainable and often cruel manipulation of the Sonoran Desert toad.

Gaps and limitations are also identified in clinical trial design include small sample sizes, lack of placebo, difficulties in blinding the psychedelic effect, expectancy bias, homogenous research participant populations, and heterogeneous trial designs. These gaps can be addressed by improved trial design and recruitment methods. Further, additional controlled trials on healthy subjects are required, and will help in the understanding of underlying mechanisms, safety and effects on consciousness, cognition and behavior. The therapeutic and threshold doses of the various psychedelic compounds remain to be confirmed, as do underlying mechanisms, aspects of neurobiology and the time periods of persisting effect.

Urgent public health concerns that require intervention at both social and individual levels, such as the toxic drug poisoning/overdose epidemic and tobacco addiction, mark an imperative to investigate solutions that mitigate public health risks and the devastating sequelae of these health conditions. Certainly, the toll of deaths and health system burdens—not to mention the sheer human tragedy—from the toxic illicit drug crisis make research into substance use disorder a priority. Additional research on tobacco cessation would also seem important given the promising work to date and the significant health-related costs from tobacco use. While our review did not explicitly include behavioural addictions such as Internet Gaming Disorder or Gambling Use Disorder these are other potential areas for fruitful investigation. Continued research with ibogaine for support in opioid withdrawal is also suggested by previous findings, beginning first with a consensus panel on dosage and screening/safety protocols. Applications of ketamine are also warranted given promising findings across multiple substances including cocaine, stimulant use disorder being particularly challenging to treat.

Psychedelic research trials into depression and anxiety disorders could help develop promising and novel forms of therapy for these two highly prevalent conditions. Given the mixed results of currently approved pharmacotherapies for mental health conditions, and the high rates of treatment resistance or challenging side effects, new evidence-based interventions are required in addition to standard contemporary therapies. The evidence so far clearly indicates the synergistic effect of *combining* effective pharmacotherapies along with psychotherapy or other psychological supports. This naturally extends to psychedelic pharmacotherapies, which are likely to increase in safety and efficacy when combined with appropriate and effective psychotherapeutic protocols. Research into differing models of psychedelic-assisted therapies is also warranted, especially in MDMA for PTSD, given the high-cost and time commitments of the MAPS-sponsored manualized therapy for PTSD.

Given the rapid rise of public interest in psychedelics, and considering the progress made to-date in obtaining regulatory approval, the educational, knowledge translation, and capacity development needs of health care providers in Canada requires a strategic response. This includes additional training and certification of psychotherapists, psychologists, psychiatrists, mental health counsellors, nurses, nurse practitioners, physicians, pharmacists, Registered Massage Therapists, Rehabilitation and Occupational therapists, yoga therapists, spiritual care providers, and other disciplines that may facilitate or complement psychedelic-assisted therapies. Core competencies, best practices, a code of ethics and practice standards remain to be developed, as does the regulatory oversight of psychedelic therapy practitioners. Evaluation of training and quality improvement initiatives are essential.

Pre-clinical research including animal and in vivo studies, botanical, and chemical analyses, along with the expansion of research into psychedelics among healthy volunteers is also required. Such research aids in developing knowledge of underlying mechanisms in addition to safety. Neuroimaging studies assist in understanding the physiological processes and neuroanatomical regions at play in psychedelic therapy, helping to shape an understanding of underlying mechanisms of change and shedding new light on the nature of consciousness and of mental health in general. Indeed, several fMRI studies with psychedelics conducted over the past two decades have contributed highly insightful findings into the etiology of depression, which may translate into more effective treatment and prevention.

Population health research is also needed to establish surveillance systems that would both track any public health risks associated with increased population-level use of psychedelics, and measure potential benefits to well-being.

Knowledge synthesis as well as knowledge exchange and transfer are critical to the development of accurate public information regarding psychedelics. Developing 'lower risk use guidelines,' such as those that exist for alcohol and cannabis, can be replicated for psychedelics, facilitating public safety, and minimizing risks and harms.

From a population health perspective, certain communities carry a high burden of preventable illness and of psychiatric co-morbidity due to social marginalization and structural violence. To ensure that psychedelic-related policy and treatments are embedded within a public health equity framework, there is a need to recognize priority populations such as people who use

substances that expose them to a toxic drug supply, historically oppressed and marginalized communities, LGBTQ2S+ communities, and racialized peoples who regularly experience microaggressions.

Other considerations identified in this review include: the need to ease the administrative and bureaucratic burden to using psychedelics as research compounds, the need to continue to develop information regarding the relative safety profiles of the various psychedelics, the need for economic impact evaluations, the importance of using mixed methods to explore issues of set and setting, the need for naturalistic studies, and the need for health and public policy analyses.

8.1 Future Ketamine-Specific Trial Design Considerations

Given the large volume of clinical trial publications, we chose to synthesize the ketamine literature separately in order to yield specific, evidence-based suggestions for future ketamine trial design. The NMDA antagonist properties of ketamine are thought to contribute to its demonstrated antidepressant effects. Since other NMDA antagonists without psychoactive properties have not demonstrated antidepressant effects, future studies exploring pharmacological properties of ketamine are needed (Grabski et al., 2020). The psychoactive properties that occur during or soon after ketamine administration (dissociative/psychotomimetic and mystical effects) may contribute to beneficial effects (Grabski et al., 2020). Designing best practice standards and training requires a better understanding of whether positive outcomes are the result of these effects alone or whether a certain supportive set/setting are needed as well (Grabski et al., 2020). Grabski et al. (2020) also postulates that, if the psychoactive effects of ketamine are not related to outcomes, then other medications similar to ketamine could be formulated but without the psychoactive properties (which, the authors note, could be unsettling for some).

A summary of Grabski et al.'s (2020) five recommendations related to future studies of ketamine's psychoactive properties are:

1. Ensure that studies are adequately powered and that an *a priori* hypothesis is listed before collecting data.
2. Focus on replicating earlier findings as well as designing standardized study protocols that are consistent in the amount of ketamine given, when assessments are done, patient qualities, rating scales (practitioner vs. self), etc.
3. Report statistics with each study and report them completely (including measures of effect size, spread and skew).
4. Develop new assessment tools for assessing psychotomimetic effects and use suitable ones in the meantime (i.e., Psychotomimetic States Inventory).
5. Assess the role of set and setting in future studies more thoroughly.

As previously discussed, it has been noted that the definition of treatment-resistant depression (TRD) is not standardized in ketamine studies and/or is evolving. Thus, RCTs and/or reviews examining the efficacy of ketamine for TRD are difficult to effectively synthesize (Bahji et al., 2021; Grabski et al., 2020; Papakostas et al., 2020). Bahji et al. (2021) also noted that ketamine's effectiveness in individuals without TRD is not known. In future studies, it would be valuable to ensure that the most up-to-date diagnostic assessments are used (for instance, the MGH Antidepressant Treatment Questionnaire) (Papakostas et al., 2020).

Comparison of IV and IN ketamine is another area of future research. McIntyre et al. (2020) suggest that a "head-to-head adequately powered controlled study...would help answer questions of efficacy, safety/tolerability, acceptability, adherence and cost-benefit". Bahji et al. (2021) concurs, noting that additional head-to-head studies are needed comparing IV racemic ketamine and esketamine since they found that, at the subgroup level, differences were not significant. Papakostas et al. (2020) also encourages more studies to determine "actual difference" in efficacy between IV esketamine and IN esketamine and, if results point in favour of IV, then they suggest studies examining effectiveness, harmlessness, and tolerability of reaching and sustaining remission with IV esketamine vs IN. Studies examining IN esketamine alone vs esketamine combined with nonpharmacologic methods of reducing depression (e.g., psychotherapy, transcranial magnetic stimulation, natural methods etc.) may be important, especially for those wishing to avoid the side effects of common antidepressants (Papakostas et al., 2020).

Future studies could also assess other routes of administration of ketamine. For instance, oral, IM, and SC formulations, if shown to be efficacious, may be more readily accepted by clients rather than IV infusions. Cavenaghi et al. (2021) explained that there is not enough data about SC racemic ketamine and esketamine for depression nor information comparing SC with IV or IN methods. They also indicate a need for data about the cost-effectiveness of SC ketamine as well as more studies in general comparing variables among routes of administration. In terms of costs, SC esketamine was estimated at approximately \$2.70 USD per 2 ML ampoule (2 dosages) whereas IN esketamine ranges from \$5664-\$8142 USD for the first month, and IV racemic ketamine is about \$500-\$1000 USD per session (Cavenaghi et al., 2021). Studies exploring access to ketamine therapy related to cost would be valuable.

The use of IM, oral, and sublingual ketamine for suicidal ideation require more investigation according to Xiong et al. (2021). As well, Maguire et al. (2021) suggest research about ketamine use for suicidal ideation in the emergency room and noted that neither IN ketamine nor IN esketamine had been studied in that setting. They also suggest adequate control groups and larger samples with inclusion of common co-morbidities to ensure representative samples.

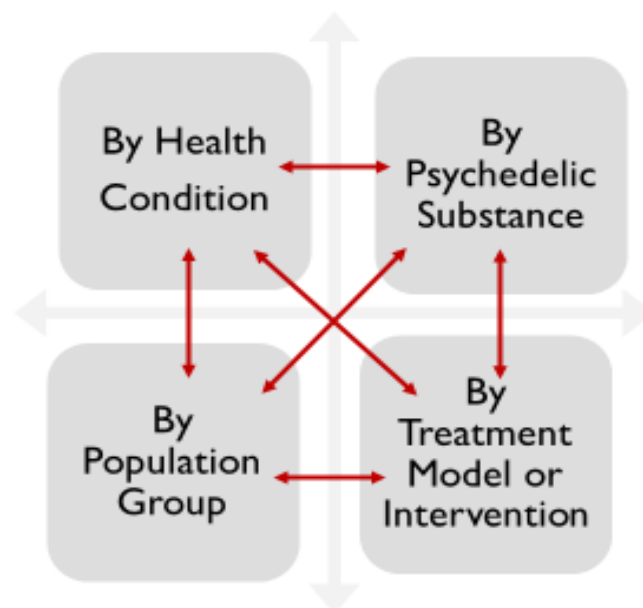
Ketamine-assisted psychotherapy has been shown to be helpful for treating dependency on alcohol and opiates (CNS depressants) and, therefore, may also be effective for treating dependency on benzodiazepines and/or barbiturates (Krupitsky et al., 2007b). It has also been shown to be effective for treating dependency on CNS stimulants like ephedrine and therefore may augment usual treatment for nicotine, caffeine, cocaine, and amphetamine dependence (Krupitsky et al., 2007b).

Lastly, we point again to the recent work situating a ketamine treatment protocol within a traditional Indigenous healing context (Muscat et al., 2021) not only as a future direction for ketamine research but as an exemplary model for culturally attuned psychedelic-assisted therapy that could be adapted to other psychedelics.

8.2 A Framework to Support Prioritization and Future Consultation

Given the complexity of the field, the many possible avenues for research at this time, and the need to be strategic with limited resources, we offer a conceptual framework in support of prioritization and future consultation related to therapeutic use of psychedelics (Figure 3). Prioritizing among **health conditions** could consider burden of disease, efficacy of current treatment and support, Return-on-Investment, as well as current research capacity and priorities in Canada. Prioritizing by **population** could consider current gaps in the knowledge base, noting for example the dearth of studies exploring gender, sex and age differences, and the need to prioritize within and across BIPOC populations, including Indigenous peoples and marginalized populations in general. Psychedelic **substances** could be prioritized based on where the field is at in terms of progress through Phase 1, 2 and 3 trials, as well as status of regulatory opportunities for research and agreements on safety protocols. Lastly, one could prioritize by type of **treatment model**, including hybrid models and account for factors such as workforce capacity with required competencies, relative cost-effectiveness, and equity considerations with respect to eventual access to evidence-based interventions.

FIGURE 3. A FRAMEWORK FOR IDENTIFYING AND PRIORITIZING RESEARCH GAPS AND OPPORTUNITIES ACCORDING TO ANALYTIC GROUPINGS



In Table 2 we offer a suggested starting place for future conversation based on consideration of the factors identified above in the 2 x 2 framework. Of course, the real challenge will be drilling down on the multitude of possibilities. To support that process we suggest starting with **health conditions** and **psychedelic substance** and then narrowing down from there based on population group and type of treatment model or intervention.

TABLE 2. SUGGESTED PRIORITY AREAS WITHIN THE FOUR DOMAINS

<p><i>Suggestions for prioritizing within health condition</i></p> <ul style="list-style-type: none"> - Substance use disorders - Depressive and anxiety disorders <ul style="list-style-type: none"> o Mood o PTSD o End of life distress o OCD - Eating disorders/BDD - Neurological/organic <ul style="list-style-type: none"> o Pain and headache o Stroke recovery 	<p><i>Suggestions for prioritizing by psychedelic substance</i></p> <ul style="list-style-type: none"> - MDMA - Psilocybin - Ketamine - Ayahuasca - DMT - 5-MeO-DMT - Ibogaine - Mescaline/peyote
<p><i>Suggestions for prioritizing within population sub-groups</i></p> <ul style="list-style-type: none"> - Women and gender issues - Age including youth and older adults - BIPOC, including Indigenous People and other marginalized (e.g., homeless) - Veterans, First Responders and Health Care Workers 	<p><i>Suggestions for prioritizing within treatment models and interventions</i></p> <ul style="list-style-type: none"> - Alternative approaches for psychedelic-assisted therapy, including ritualistic approaches - Post-intervention integration strategies <ul style="list-style-type: none"> o Therapist assisted o Peer and family-support o Virtual - Mixed treatment models (e.g., combining with neurofeedback, mindfulness, Acceptance and Commitment therapy, ritualistic) - Evaluation of training and certification

8.3 Supporting Population Health Research

In addition to these four groupings for prioritization, we suggest a strong effort with respect to population health research including the development of multi-component surveillance systems to assess potential risks and harms related to increased use of psychedelics in the general population. Such a system would include an equal emphasis on identifying safe practices and potential benefits for psychological well-being and prevention, including suicidality. These studies may provide important clues for clinical research, for example, assessment of adverse

events as well as measurement of beneficial side effects. Lower-risk guidelines for psychedelic use are required for public education and harm reduction purposes. Given the active grey market in magic mushroom sales in Canada, lower-risk guidelines would assist in reducing the known possible adverse effects of naturalistic psychedelic use.

8.4 Maximizing Canadian Capacity and Encouraging Collaboration

There is no question that the field of psychedelic science has re-emerged very rapidly, clearly attested by the sheer volume of literature identified by the writing team, which does not include the work on basic psychopharmacology and neuroscience. In Canada this resurgence has occurred in parallel to international interest, with signs of support by the Federal government, such as the groundbreaking religious exemptions granted to Santo Daime and CDSA exemptions for medical psilocybin use as well as recent funding initiatives by CIHR. Key institutions that support this work include CCSA, MHCC, and CAMH, best illustrated by their collaboration on the May 2022 Research to Reality conference in Toronto, as well as several prestigious universities. Last, but not least, the excellence and diversity of the Canadian research community in mental health and substance use has been a vital source of support.

It is natural in a burgeoning field of such high interest and potential that duplication may emerge, if not outright competition for scarce resources for research and development. To minimize these challenges, we would encourage some of the following activities:

- Key institutions such as CCSA, MHCC, and CAMH, perhaps with CIHR and Health Canada and SSHRC support, initiate a formal asset mapping exercise to identify current strengths, weaknesses, opportunities, and challenges in the areas of clinical, neuroscience, epidemiology and population health, health policy, research ethics and diversity.
- Encourage collaboration through multi-site clinical trials so as to maximize power and generalizability.
- Initiate a dialogue with Canada's Indigenous peoples to gauge level of support for work in this area and how they may be engaged as equal partners in a culturally attuned way.
- Develop research training opportunities for students and post-doctoral fellowships.
- Articulate an action plan to create a productive, ethical relationship with private industry which is rapidly expanding its Canadian footprint for psychedelic-assisted treatment.
- Through ongoing evaluation, confirm national guidelines for training and certification of clinicians and facilitators who will be needed both for clinical trials as well in practice settings, pending approvals. This should include evaluation of the role of people with lived experience, for example, as peer facilitators.

- Large, multi-site clinical trials of sufficient power are required, and the current infrastructure and capacity of organizations like the Canadian Cancer Trials Group could serve as a template for their development and planning in Canada.

9.0 Conclusion and Next Steps

It is some two generations past, in the 1970s, that psychedelic substances were put under regulatory controls so stringent that they were effectively banned from use in a therapeutic or research context, despite sufficient evidence that scholars agreed should have supported further research. Since the early 2000s, but particularly in the last decade, there has been a rapid resurgence of interest in these substances, spurred on not only by a re-assessment of that earlier research but also the scope of the global health burden and societal costs associated with mental and substance use disorders. Further incentive comes from the challenges that remain in the therapeutic toolkit for a large number of those in need. Aside from needed therapeutic advances for these mental and substance use-related challenges, this work also holds promise for unlocking important basic neurobiological mechanisms that may help with other mental and physical health conditions. It may also hold promise for supporting overall health and wellbeing.

This rapid review of the clinical application of psychedelics has been vast in its breadth and ambitious in its intent to meaningfully synthesize diverse bodies of clinical and other research. Given the narrative structure of our reporting, results by health condition or by psychedelic compound would benefit from further analysis, meta-analysis, assessment of the quality of the literature, and more robust discussion. Consultation with external and relevant stakeholders regarding the results of this knowledge synthesis exercise would be of great benefit in knowledge translation, in the further interpretation of results, and in the development of Canadian psychedelic research priorities, including further identification of needs, gaps and opportunities. We suggest this consultation process as an important next step and suggest robust and open dialogue with Indigenous leaders, Elders, researchers and community members to work through many of the areas where divergence of opinion may bear fruit through an openness to learn from each other and develop common ground.

There is every indication that research in this area will continue to accelerate both domestically within Canada and on a global scale. This highlights the need for a common research agenda. There is also a need for research synthesis and knowledge translation activities that would engage diverse stakeholders. These include clinicians, policy makers, Indigenous peoples and people with lived and living experience whose perspectives will maximize the relevance of the research questions being addressed and lead to rapid translation of the ensuing evidence to both healthy policy and clinical practice.

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Appendices

Appendix 1: Table of Current Psychedelic Registered Trials (as of August 24, 2021)

Trial Name	Completed	Registered	In process	Indication	Psychedelic Medicine	Country	Institution	PI	Trial Design	Phase 1	Phase 2	Phase 3	#Cohort	Research Question/Objective?
A Double-Blind Trial of Psilocybin-Assisted Treatment of Alcohol Dependence		X		Alcoholism	Psilocybin	United States	NYU Langone Health	Michael Bogenschutz	Randomized, double-blind, parallel assignment		X		135	To contrast the acute and persisting effects of psilocybin to those of diphenhydramine in the context of outpatient alcoholism treatment
Effects and Therapeutic Potential of Psilocybin in Alcohol Dependence				Alcoholism	Psilocybin	Mexico	University of New Mexico	Michael Bogenschutz	Open-label, single group assignment		X		10	To assess the effects of psilocybin in alcohol dependent participants, demonstrate the feasibility of the integrated behavioral/pharmacologic intervention, and provide preliminary outcome and safety data
Pilot Trial of Visual Healing®, a Nature-themed Virtual Immersive Experience, to Optimize Set and Setting in Psilocybin-assisted Therapy for Alcohol Use Disorder			X	Alcoholism	Psilocybin	United States	Pacific Treatment & Research in Psychedelics	Keith Heinzerling	Randomized, open-label, parallel assignment		X		20	To evaluate the feasibility, safety, and tolerability of adding Visual Healing, a nature-themed virtual immersive program, to psilocybin-assisted therapy among participants with alcohol use disorder
Phase II, Randomized, Double Blind, Placebo Controlled, Parallel Group, Single Center Study of Psilocybin Efficacy and Mechanism in Alcohol Use Disorder			X	Alcoholism	Psilocybin	Switzerland	University of Zurich	Katrin Preller	Randomized, double blind, placebo controlled, parallel assignment		X		60	To evaluate effects of psilocybin on alcohol use behaviour, clinical symptoms, neurocognitive and emotional measures in patients with alcohol use disorder
Psilocybin for Treatment of Alcohol Use Disorder: a Feasibility Study		X		Alcoholism	Psilocybin	Denmark	Psychiatric Center Copenhagen, Rigshospitalet	Anders Fink-Jensen	Open-label, single group assignment		X		10	To assess the feasibility and safety of administering a single dose of psilocybin to patients diagnosed with alcohol use disorder (AUD)
Open-Label Proof of Concept Feasibility Study to Explore the Safety, Tolerability and Potential Role of MDMA-Assisted Psychotherapy for the Treatment of Detoxified Patients With Alcohol Use Disorder		X		Alcoholism	MDMA	England	Imperial College of London	David Nutt	Open-label	X			20	To investigate the safety, tolerability and role of MDMA-assisted psychotherapy for the treatment of detoxified patients with Alcohol Use Disorder
Tolerability and Efficacy of Ibogaine in the Treatment of Alcoholism: the First Randomized, Double-blind, Placebo-controlled, Escalating-dose, Phase 2 Trial		X		Alcoholism	Ibogaine	Brazil	Ribeirao Preto Medical School	Rafael dos Santos	Randomized, double-blind, placebo-controlled		X		12	To evaluate the safety, tolerability and efficacy of increasing doses of ibogaine in 12 alcoholic patients
Effects of Psilocybin in Anorexia Nervosa			X	Anorexia Nervosa	Psilocybin	United States	Johns Hopkins University	Roland Griffiths	Open-label, single group assignment	X			18	To investigate the safety and efficacy of psilocybin in persons with chronic anorexia nervosa (AN)
Psilocybin as a Treatment for Anorexia Nervosa: A Pilot Study			X	Anorexia Nervosa	Psilocybin	England	Imperial College of London	Meg Spriggs	Open-label, single group assignment	X	X		20	To assess the acceptability and efficacy of treating anorexia nervosa with psilocybin, and to use Magnetic Resonance Imaging (MRI) and Electroencephalography (EEG) to examine the neuronal underpinnings of treatment with psilocybin in this patient group.

Evaluation of Psilocybin in Anorexia Nervosa: Safety and Efficacy			X	Anorexia Nervosa	Psilocybin	United States	University of California, COMPASS Pathways	Stephanie Knatz Peck	Open-label, single group assignment		X		20	To assess the safety and tolerability of one 25 mg dose of psilocybin in participants with anorexia nervosa based on adverse events (AEs), changes in vital signs, electrocardiograms (ECGs) and clinical laboratory tests
LSD Treatment in Persons Suffering From Anxiety Symptoms in Severe Somatic Diseases or in Psychiatric Anxiety Disorders: a Randomized, Double-blind, Placebo-controlled Phase II Study			X	Anxiety	LSD	Switzerland	University Hospital, Basel, Switzerland	Matthias Liechti & Patrick Dolder	Randomized, double-blind, placebo-controlled, crossover		X		40	To test the efficacy of LSD in patients with anxiety with or without life-threatening diseases.
Randomized Double Blind Placebo Controlled Assessing the Efficacy of Micro-dosed Psilocybin in Reducing Anxiety and or Depression Levels in Adults		X		Anxiety and Depression	Psilocybin	Jamaica	Wake Network	Roger Gibson	Randomized, double-blind, placebo-controlled, parallel assignment		X		120	To investigate the efficacy of a 16 week treatment with PSIL428 patient reported anxiety levels in otherwise healthy individuals suffering from depression and or anxiety symptoms
A Placebo-controlled, Randomized, Blinded, Dose Finding Phase 2 Pilot Safety Study of MDMA-assisted Therapy for Social Anxiety in Autistic Adults	X			Autism Spectrum Disorder	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Charles Grob	Randomized, blinded, placebo-controlled		X			To assess the safety and feasibility of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy for social anxiety in MDMA-naïve adults on the autism spectrum
The Safety and Efficacy of Psilocybin in Participants With Type 2 Bipolar Disorder (BP-II) Depression			X	Bipolar Disorder	Psilocybin	United States	Sheppard Pratt Health System	Scott Aaronson	Open-label, single group assignment		X		12	To evaluate the efficacy of 25 mg of psilocybin under supportive conditions to adult participants with BP-II, current episode depressed, in improving depressive symptoms
Safety and Efficacy of Psilocybin for Body Dysmorphic Disorder			X	Body Dysmorphic Disorder	Psilocybin	United States	New York State Psychiatric Institute	Franklin Schneier	Open-label, single group assignment		X		12	To investigate the efficacy of a single oral dose of psilocybin in treating adult outpatients with body dysmorphic disorder that have not responded to at least one adequate trial of a serotonin reuptake inhibitor
Psilocybin-assisted Group Therapy for Demoralization in Long-term AIDS Survivors	X			Demoralization in AIDS	Psilocybin	United States	University of California	Joshua Woolley	Open-label, single group assignment	X			30	To determine whether psilocybin-assisted group psychotherapy is a safe and feasible treatment for demoralization in long-term AIDS survivors (LTAS)
Psilocybin Therapy for Depression and Anxiety in Parkinson's Disease: a Pilot Study			X	Depression and Anxiety Related to Parkinson's	Psilocybin	United States	University of California	Joshua Woolley	Open-label, single group assignment		X		10	To determine the safety, tolerability, and feasibility of psilocybin therapy for depression and anxiety in people with Parkinson's disease
Pilot Study of Serotonin 2A Receptor (5-HT _{2A}) Agonist Psilocybin for Depression in Patients With Mild Cognitive Impairment or Early Alzheimer's Disease			X	Depression	Psilocybin	United States	Johns Hopkins University	Albert Garcia-Romeu	Open-label, single group assignment	X			20	To evaluate the potential efficacy of psilocybin to produce improvement in depression compared to pre-treatment in people with Mild Cognitive Impairment (MCI) or early Alzheimer's Disease (AD) and clinically significant symptoms of depression
Antidepressant Effects of Ayahuasca: a Randomized Placebo Controlled Trial in Treatment Resistant Depression	X			Depression	Ayahuasca	Brazil	Universidade Federal do Rio Grande do Norte	Draulio Araujo	Randomized, placebo-controlled	X	X		35	To test the efficacy of Ayahuasca in treatment-resistant depression.
Fixed Order, Open-Label, Dose-Escalation Study of DMT in Humans			X	Depression, Major Depressive Disorder	DMT	United States	Yale University	Deepak D'Souza	Non-randomized, open-label	X			6	To investigate the safety and efficacy of specific doses of dimethyltryptamine (DMT) in humans.

A Phase 1/2 Study of GH001 in Patients With Treatment-Resistant Depression			X	Depression	DMT	Netherlands	GH Research Limited	GH Research Clinical Team	Open-label, non-randomized	X	X		16	to investigate the safety of GH001 (containing 5-methoxy-dimethyltryptamine; 5-MeO-DMT), and to investigate its effects on severity of depressive symptoms, and its dose-related psychoactive effects in patients with Treatment-Resistant Depression (TRD)
Psilocybin and Depression - Assessing the Long-term Effects of a Single Administration of Psilocybin on the Psychiatric Symptoms and Brain Activity of Patients With Severe Depression		X		Depression	Psilocybin	Finland	University of Helsinki	Tomi Rantamäki	Randomized, double-blind, placebo-controlled, parallel assignment		X		60	To investigate the possible long-term therapeutic effects of psilocybin on the symptoms of severe depression, as well as the brain mechanisms underlying these changes
Circulating Oxytocin Changes in Response to the Oxytocin System Stimulator MDMA in Patients With Diabetes Insipidus and Healthy Controls			X	Diabetes Insipidus	MDMA	Switzerland	University Hospital, Basel	Mirjam Christ-Crain	Randomized, double-blind, placebo-controlled				30	To evaluate oxytocin levels in response to MDMA administration as compared to placebo in patients with diabetes insipidus and healthy volunteers
An Open-Label, Multi-Site Phase 2 Study of the Safety and Feasibility of MDMA-Assisted Psychotherapy for Eating Disorders		X		Eating Disorders	MDMA	N/A	Multidisciplinary Association for Psychedelic Studies	Corine de Boer	Open-label, non-randomized		X		36	To explore the safety and feasibility of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy and adjunctive caregiver involvement in the treatment of 18 participants with eating disorders
A Randomized, Double-Blind, Placebo-Controlled Phase 2 Pilot Study of MDMA-Assisted Psychotherapy for Anxiety Associated With a Life-Threatening Illness	X			End-of-Life Distress	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Philip Wolfson	Randomized, double-blind, placebo-controlled, parallel assignment		X		18	To compare the effects of MDMA-assisted therapy vs. placebo with therapy in 18 patients with anxiety related to a life-threatening illness
Psilocybin for Psychological and Existential Distress in Palliative Care: A Multi-site, Open-label, Single Arm Phase 1/2 Proof-of-concept, Dose-finding, and Feasibility Clinical Trial			X	End-of-Life Distress	Psilocybin	Canada	Ottawa Hospital Research Institute	James Downar	Open-label	X	X		40	To determine the safety, feasibility, therapeutic dose, and preliminary efficacy of psilocybin microdosing to treat psychological distress among patients with advanced illness
Pilot Study of Psilocybin-Assisted Therapy for Demoralization in Patients Receiving Hospice Care - PATH Study		X		End-of-Life Distress	Psilocybin	United States	Dana-Farber Cancer Institute	Yvan Beaussant	Open-label, single group assignment		X		15	To develop and pilot test a novel regimen of psilocybin-assisted psychotherapy for demoralization in patients receiving hospice care
A Pilot Study of Psilocybin Enhanced Group Psychotherapy in Patients With Cancer		X		End-of-Life Distress	Psilocybin	United States	University of Utah	Paul Thielking	Open-label, single group assignment	X			12	To assess the effects of offering psilocybin to patients in group therapy for cancer
Psychopharmacology of Psilocybin in Cancer Patients	X			End-of-Life Distress	Psilocybin	United States	Johns Hopkins University	Roland Griffiths	Randomized, double-blind, crossover design		X		56	To find out if psilocybin can produce personally and spiritually meaningful experiences in cancer patients
Effects of Psilocybin in Advanced-Stage Cancer Patients With Anxiety	X			End-of-Life Distress	Psilocybin	United States	Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center	Charles Grob	Non-randomized, double-blind, single group assignment	X			12	To measure the effectiveness of the novel psychoactive medication psilocybin on the reduction of anxiety, depression, and physical pain

Effects of Psilocybin on Anxiety and Psychosocial Distress in Cancer Patients	X			End-of-Life Distress	Psilocybin	United States	NYU Langone Health	Stephen Ross	Randomized, double-blind, active placebo-controlled, crossover assignment	X			29	To assess the efficacy of psilocybin administration (4-phosphoryloxy-N,N-dimethyltryptamine), a serotonergic psychoactive agent, on psychosocial distress, with the specific primary outcome variable being anxiety associated with cancer
Safety and Efficacy of Lysergic Acid Diethylamide (LSD) as Treatment for Cluster Headache: a Randomized, Double-blind, Placebo-controlled Phase II Study)			X	Headache	LSD	Switzerland	University Hospital, Basel, Switzerland	Matthias Liechti & Yasmin Schmid	Double-blind, randomized, placebo-controlled two-phase crossover study design		X		30	To investigate the effects of an oral LSD pulse regimen (3 x 100 µg LSD in three weeks) in patients suffering from CH compared with placebo.
Safety and Efficacy of Psilocybin for the Treatment of Headache Disorders: Sub-Study I		X		Headache	Psilocybin	United States	Yale University	Deepak Cyril D'Souza	Randomized, double-blind, placebo-controlled, crossover assignment	X			24	To investigate the effects of different doses of oral psilocybin in migraine headache
Repeat Dosing of Psilocybin in Headache Disorders			X	Headache	Psilocybin	United States	Yale University	Emmanuelle Schindler	Randomized, double-blind, placebo-controlled, parallel assignment	X			24	To investigate the efficacy of single and repeated doses of psilocybin in the treatment of migraine headache, as well as identifying the underlying mechanisms of psilocybin's effects by measuring neuroinflammatory markers for migraine headache
Prophylactic Effects of Psilocybin on Chronic Cluster Headache: an Open-label Clinical Trial and Neuroimaging Study			X	Headache	Psilocybin	Denmark	Neurobiology Research Unit, Rigshospitalet	Gitte Moos Knudsen	Open-label, single group assignment	X	X		20	To investigate the prophylactic effects of a low dose of psilocybin in chronic cluster headache
Safety and Efficacy of Psilocybin for the Treatment of Headache Disorders: Sub-Study II			X	Headache	Psilocybin	United States	Yale University	Deepak Cyril D'Souza	Randomized, double blind, placebo controlled, crossover assignment	X			24	To investigate the effects of two different doses of oral psilocybin in post-traumatic headache
Safety and Efficacy of Psilocybin for the Treatment of Headache Disorders			X	Headache	Psilocybin	United States	Yale University	Emmanuelle Schindler	Randomized, double-blind, placebo-controlled, crossover design	X			24	To investigate the effects of an oral psilocybin pulse regimen of two different doses in alleviating symptoms of cluster headache
An Exploratory Open-Label, Phase 1b, Ascending Dose Study to Evaluate the Effects of Oral 3-[2-(Dimethylamino)Ethyl]-1h-indol-4-yl Dihydrogen Phosphate (Psilocybin, BPL-PSILO) on Cognition in Patients With Chronic Short-Lasting Unilateral Neuralgiform Headache Attacks (SUNHA)			X	Headache	Psilocybin	United Kingdom	Beckley Psytech	Kasia Kabow	Open-label, single group assignment	X			12	To evaluate the effects of psilocybin on cognition in patients with Chronic Short-Lasting Unilateral Neuralgiform Headache Attacks (SUNHA)
LSD Therapy for Persons Suffering From Major Depression: A Randomised, Double-blind, Active-placebo Controlled Phase II Study			X	Major Depression	LSD	Switzerland	University Hospital, Basel, Switzerland	Stefan Borgwardt & Matthias Liechti	Randomised, double-blind, active-placebo-controlled trial		X		60	To test the efficacy of LSD in patients with Major Depressive Disorder.

A Randomized, Double-Blind, Support-of-Concept Phase 2 Study of Single-Dose Psilocybin for Major Depressive Disorder (MDD)			X	Major Depression	Psilocybin	United States	Usona Institute	Charles Raison	Randomized, double-blind, parallel assignment		X		100	To evaluate the potential efficacy of a single 25 mg oral dose of psilocybin for MDD compared to the active placebo in otherwise medically-healthy participants, assessed as the difference between groups in changes in depressive symptoms from Baseline to Day 43 post-dose
The Safety and Efficacy of Psilocybin in Cancer Patients With Major Depressive Disorder			X	Major Depression	Psilocybin	United States	Maryland Oncology Hematology	Manish Agrawa	Open-label, single group assignment		X		30	To explore the safety, tolerability and efficacy of a 25mg dose of psilocybin in cancer patients with major depressive disorder (MDD)
Psilocybin-Induced Neuroplasticity in the Treatment of Major Depressive Disorder			X	Major Depression	Psilocybin	United States	Yale University	Deepak Cyril D'Souza	Randomized, double-blind, placebo-controlled, crossover assignment	X			18	To investigate whether psilocybin alters neuroplasticity in people with major depressive disorder
Effects of Psilocybin in Major Depressive Disorder	X			Major Depression	Psilocybin	United States	Johns Hopkins University	Roland Griffiths	Randomized, single-blind, parallel assignment		X		24	To investigate acute and persisting effects of psilocybin on depressive symptoms and other moods, attitudes, and behaviors
Phase II, Randomized, Double Blind, Placebo Controlled, Parallel Group, Single Center Study of Psilocybin Efficacy in Major Depression			X	Major Depression	Psilocybin	Switzerland	University of Zurich	Franz Vollenweider	Randomized, double-blind, placebo-controlled, parallel assignment		X		60	To determine the effects of serotonin 2A/1A receptor stimulation by psilocybin on mood and emotion processing in major depressive disorder
Psilocybin Treatment of Major Depressive Disorder With Co-occurring Alcohol Use Disorder			X	Major Depression & Alcoholism	Psilocybin	United States	Johns Hopkins University	Frederick Barrett	Randomized, double blind, placebo controlled, parallel assignment		X		90	To determine whether psilocybin, a hallucinogenic drug, is effective in reducing depressive symptoms and amount of drinking in patients with co-occurring Major Depressive Disorder (MDD) and Alcohol Use Disorder (AUD)
Open Label, Phase 1 Study for Evaluating the Feasibility, Safety and Efficacy of Psychotherapy Assisted Psilocybin for Treatment of Severe OCD		X		Obsessive-Compulsive Disorder	Psilocybin	N/A	Beersheva Mental Health Center	N/A	Open-label, single group assignment	X			15	To investigate the feasibility, safety and efficacy of psychotherapy assisted psilocybin for treatment of severe OCD
Psilocybin for Treatment of Obsessive Compulsive Disorder		X		Obsessive-Compulsive Disorder	Psilocybin	United States	University of Arizona	Francisco A. Moreno	Randomized, parallel assignment, phase 1 is double-blind and phase 2 is single-blind	X	X		15	To evaluate whether psilocybin, a hallucinogenic drug, improves symptoms of obsessive compulsive disorder (OCD), whether it is safely tolerated as treatment of OCD, and will investigate the mechanisms by which it works
Psilocybin Treatment in Obsessive-Compulsive Disorder: a Preliminary Efficacy Study and Exploratory Investigation of Neural Correlates			X	Obsessive-Compulsive Disorder	Psilocybin	United States	Yale University	Benjamin Kelmendi	Randomized, double-blind, placebo-controlled, parallel assignment	X			30	To investigate the effects of oral psilocybin on OCD symptomatology and provide the first evidence of the neural mechanism that may mediate psilocybin's purported therapeutic effects on OCD
The Effects of MDMA on Prefrontal and Amygdala Activation in Posttraumatic Stress Disorder			X	PTSD	MDMA	United States	Yale University	Benjamin Kelmendi	Double-blind, placebo-controlled, within-subjects, crossover-dose	X			20	To investigate the effects of MDMA on prefrontal and amygdala activation, and to explore the relationship between these MDMA-induced neural changes and the acute behavioral effects of the drug in patients with PTSD
An Open-Label, Phase 2, Multicenter Feasibility Study of Manualized MDMA-Assisted Psychotherapy With an Optional fMRI Sub-Study Assessing Changes in Brain Activity in Subjects			X	PTSD	MDMA	Netherlands	MAPS Europe B.V.	Eric Vermetten	Open-label, non-randomized		X		40	To gather supportive data on the safety and effectiveness of manualized MDMA-assisted psychotherapy as a treatment for PTSD

With Posttraumatic Stress Disorder														
An Open-Label, Multi-Site Phase 2 Study of the Safety and Effect of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder	X			PTSD	MDMA	Canada	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Open-label		X		4	To assess the safety and effect of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in participants diagnosed with at least severe posttraumatic stress disorder (PTSD)
A Multi-Site Open-Label Safety Extension Study of Manualized MDMA-Assisted Psychotherapy for the Treatment of Participants With Posttraumatic Stress Disorder			X	PTSD	MDMA	United States & Canada	Multidisciplinary Association for Psychedelic Studies	Corine de Boer	Open-label		X		100	To assess the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy in participants who were enrolled in a parent study for treatment of posttraumatic stress disorder (PTSD)
An Open-Label, Multi-Site Phase 2 Study of the Safety and Effect of Manualized MDMA-Assisted Therapy for the Treatment of Severe Posttraumatic Stress Disorder	X			PTSD	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Open-label		X		38	To assess the safety and effect of 3,4-methylenedioxymethamphetamine (MDMA)-assisted therapy in participants diagnosed with at least severe posttraumatic stress disorder (PTSD)
Open-label Phase 2 Study of MDMA-Assisted Psychotherapy in Veterans With Combat-Related, Refractory PTSD			X	PTSD	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Shannon Remick	Open-label		X		10	To test the feasibility of administering MDMA in conjunction with psychotherapy for combat-related treatment-resistant PTSD in US military veterans currently enrolled in VA
Exploring Mechanisms of Action of \pm 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy for Posttraumatic Stress Disorder (PTSD)			X	PTSD	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Randomized, triple-blind		X		10	To study biological and psychological processes that might help researchers to better understand what is taking place during low or medium dose and full dose MDMA-assisted psychotherapy treatment in people with PTSD.
A Phase 1/2 Open-Label Treatment Development Study of Methylenedioxymethamphetamine (MDMA)-Assisted Cognitive-Behavioral Conjoint Therapy (CBCT) in Dyads in Which 1 Member Has Chronic Posttraumatic Stress	X			PTSD	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Open-label, single group assignment	X	X		12	To combine methods for conducting MDMA-assisted therapy with methods from the CBCT for PTSD in order to treat 10 participants with chronic PTSD and their partners (intimate or non-intimate significant other who does not have a current diagnosis of PTSD) in order to explore whether combined treatment is effective
A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy for the Treatment of Severe Posttraumatic Stress Disorder	X			PTSD	MDMA	United States, Canada, and Israel	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Randomized, double-blind, parallel assignment		X		100	To assess the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy with placebo in participants diagnosed with at least severe posttraumatic stress disorder (PTSD)

A Randomized, Double-Blind, Placebo-Controlled, Multi-Site Phase 3 Study of the Efficacy and Safety of Manualized MDMA-Assisted Psychotherapy for the Treatment of Posttraumatic Stress Disorder of Moderate or Greater Severity			X	PTSD	MDMA	United States, Canada, and Israel	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Randomized, double-blind, parallel assignment			X	100	To assess the efficacy and safety of 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy compared to psychotherapy with placebo in participants diagnosed with at least moderate PTSD
Randomized, Triple-Blind, Phase 2 Pilot Study Comparing 3 Different Doses of MDMA in Conjunction With Manualized Psychotherapy in 24 Veterans, Firefighters and Police Officers With Chronic Posttraumatic Stress Disorder (PTSD)	X			PTSD	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Randomized, parallel assignment			X	26	To provide information on whether psychotherapy ("talk therapy") combined with the drug MDMA is safe and helpful for subjects with posttraumatic stress disorder (PTSD)
A Phase 2, Open-Label, Randomized Comparative Effectiveness Study for MDMA-Assisted Psychotherapy in U.S. Veterans With Chronic PTSD			X	PTSD	MDMA	N/A	Multidisciplinary Association for Psychedelic Studies	Rachel Yehuda	Open-label, randomized, parallel assignment			X	60	To assess the comparative effectiveness of two versus three active MDMA-assisted sessions in U.S. military veterans with at least moderate chronic PTSD treated in an outpatient VA treatment clinic
An Open-Label Proof-of-Principle Study Testing the Use of an Additional MDMA-Assisted Psychotherapy Session in People Who Relapsed After Participating in a Phase 2 Clinical Trial of MDMA-Assisted Psychotherapy to Treat Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)	X			PTSD	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Open-label, single group assignment			X	3	To investigate the effects of an additional 3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy session in up to three participants with PTSD who relapsed after their PTSD symptoms had significantly decreased during MAPS' initial U.S. Phase 2 trial testing the use of MDMA-assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder PTSD)
A Randomized, Double-Blind, Controlled Phase 2 Pilot Study of Manualized 3,4-methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy in 12 Subjects With Treatment-Resistant Posttraumatic Stress Disorder (PTSD)	X			PTSD	MDMA	Canada	Multidisciplinary Association for Psychedelic Studies	Ingrid Pacey	Randomized, double-blind, placebo-controlled			X	6	To provide information on whether the combination of psychotherapy with the drug MDMA is safe and helpful for people with post traumatic stress disorder (PTSD)
Phase II Pilot Randomized Double-Blind Placebo-Controlled Study of 3,4-methylenedioxymethamphetamine (MDMA) Assisted Psychotherapy in Posttraumatic Stress Disorder (PTSD)	X			PTSD	MDMA	Switzerland	Multidisciplinary Association for Psychedelic Studies	Peter Oehen	Randomized, double-blind, placebo-controlled			X	14	To examine whether three six to eight-hour long sessions of methylenedioxymethamphetamine (MDMA)-assisted psychotherapy scheduled three to five weeks apart can be safely administered to participants with PTSD, and whether combining a fully therapeutic dose of MDMA with psychotherapy, when compared with a low ("active placebo") dose of MDMA, will reduce PTSD symptoms, with symptoms measured three times during the study

A Randomized, Double-Blind, Dose Response Phase 2 Pilot Study of Manualized MDMA-Assisted Psychotherapy in Subjects With Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)	X			PTSD	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Marcela d'Otalora	Randomized, double-blind, parallel assignment		X		29	To examine the safety and efficacy of MDMA-assisted psychotherapy in 23 subjects with chronic, treatment-resistant posttraumatic stress disorder (PTSD)
A Randomized, Double-Blind, Active Placebo-Controlled Phase 2 Pilot Study of MDMA-assisted Psychotherapy in People With Chronic, Treatment-Resistant Posttraumatic Stress Disorder (PTSD)	X			PTSD	MDMA	Israel	Multidisciplinary Association for Psychedelic Studies	Moshe Kotler	Randomized, double-blind, active placebo-controlled, parallel assignment		X		10	To assess the safety and efficacy of MDMA-assisted psychotherapy in 10 people with chronic, treatment-resistant posttraumatic stress disorder (PTSD), comparing the effects of low and full dose MDMA as an adjunct to psychotherapy
A Phase 2, Open Label Study of the Safety and Effectiveness of MDMA-assisted Therapy for Participants With Posttraumatic Stress Disorder		X		PTSD	MDMA	Canada	Multidisciplinary Association for Psychedelic Studies	N/A	Open-label, single group assignment		X		20	To provide supportive data on the safety and effectiveness of MDMA-assisted therapy in participants with posttraumatic stress disorder (PTSD)
Phase II Clinical Trial Testing the Safety and Efficacy of 3,4-Methylenedioxymethamphetamine (MDMA)-Assisted Psychotherapy in Subjects With Chronic Posttraumatic Stress Disorder	X			PTSD	MDMA	United States	Multidisciplinary Association for Psychedelic Studies	Michael Mithoefer	Randomized, double-blind, placebo-controlled parallel assignment		X		23	To find out if methylenedioxymethamphetamine (MDMA)-assisted psychotherapy is safe and can help people with posttraumatic stress disorder (PTSD) arising from being a victim of a crime
Psilocybin-facilitated Smoking Cessation Treatment: A Pilot Study			X	Smoking Cessation	Psilocybin	United States	Johns Hopkins University	Matthew Johnson	Randomized, open-label, parallel assignment				95	To examine psilocybin administration combined with a structured smoking cessation treatment program in nicotine dependent individuals in order to provide preliminary data on the efficacy of this combined treatment for smoking cessation
Preliminary Efficacy and Safety of Ibogaine in the Treatment of Methadone		X		Substance Abuse Disorder	Ibogaine	Spain	Hospital Universitari Sant Joan	José Bouso & Tre Borrás	Randomized, placebo-controlled		X		20	N/A
Psilocybin-Enhanced Psychotherapy for Methamphetamine Use Disorder		X		Substance Abuse Disorder	Psilocybin	United States	Portland VA Research Foundation	Chris Stauffer	Randomized, single-blind, parallel assignment	X	X		30	To assess the efficacy of psilocybin-enhanced psychotherapy as compared to treatment-as-usual among individuals being treated for methamphetamine use disorder
Psilocybin-facilitated Treatment for Cocaine Use: A Pilot Study			X	Substance Abuse Disorder	Psilocybin	United States	University of Alabama at Birmingham	Peter Hendricks	Randomized, double-blind, active placebo-controlled, parallel assignment		X		40	To evaluate the feasibility and estimate the efficacy of psilocybin-facilitated treatment for cocaine use and to monitor the impact of psilocybin-facilitated treatment on the use of other drugs and outcomes relevant to cocaine involvement (e.g., criminal involvement)
Phase I Study of the Safety and Adjunctive Effects of Psilocybin in Adults With Opioid Use Disorder Maintained on Buprenorphine/Naloxone			X	Substance Abuse Disorder	Psilocybin	United States	University of Wisconsin	Randall Brown	Open-label, single group assignment	X			10	To determine the safety of psilocybin in adult patients with opioid use disorder concurrently taking buprenorphine/naloxone (Suboxone®)

The Safety and Efficacy Of Psilocybin as an Adjunctive Therapy in Participants With Treatment Resistant Depression			X	Treatment Resistant Depression	Psilocybin	United States & Ireland	COMPASS Pathways	Guy Goodwin	Open-label, single group assignment		X		20	To explore effectiveness of 25 mg of psilocybin as an adjunctive therapy in participants with TRD
An Open Label Study of the Safety and Efficacy of Psilocybin in Participants With Treatment-Resistant Depression (P-TRD)			X	Treatment Resistant Depression	Psilocybin	United States	Sheppard Pratt Health System	Scott Aaronson	Open-label, single group assignment		X		15	To evaluate the efficacy of psilocybin (25 mg) administered under supportive conditions to adult participants with severe TRD, in improving depressive symptoms
A Randomised, Placebo Controlled Trial of Psilocybin in Treatment Resistant Depression: A Feasibility Study			X	Treatment Resistant Depression	Psilocybin	England	King's College of London	James Rucker	Randomized, double-blind, placebo-controlled, parallel assignment		X		60	To evaluate the feasibility, safety and efficacy of psilocybin, given under supportive conditions, in a randomised, blinded design in adult participants with treatment resistant major depressive disorder
The Safety and Efficacy of Psilocybin in Participants With Treatment Resistant Depression		X		Treatment Resistant Depression	Psilocybin	United States, Canada, Czechia, Denmark, Germany, Ireland, Netherlands, Portugal, Spain & the United Kingdom	COMPASS Pathways	N/A	Randomized, double-blind, parallel assignment		X		216	To evaluate the safety and efficacy of a range of psilocybin doses in patients with treatment resistant depression
A Phase II Randomized, Double-blind, Active Placebo-controlled Parallel Group Trial to Examine the Efficacy and Safety of Psilocybin in Treatment-resistant Major Depression			X	Treatment Resistant Depression	Psilocybin	Germany	Central Institute of Mental Health, Mannheim & Charite University	Gerhard Gründer	Randomized, double-blind, active placebo-controlled, parallel assignment		X		144	To investigate the safety and efficacy of oral psilocybin administered under supportive conditions in treatment-resistant major depression (TRD)

Appendix 2: List of Psychedelics

	Active Compound	Chemical Name	Classification	Source
<i>LSD</i>	LSD	lysergic acid diethylamide	Classic/Serotonergic/Ergoline	Chemical
<i>Ayahuasca</i>	DMT, beta-carbolines	N,N-dimethyltryptamine, harmaline; harmine; tetrahydroharmine	Classic/Serotonergic/Tryptamine/Indole	Plant
<i>DMT</i>	N,N-dimethyltryptamine	N,N-dimethyltryptamine	Classic/Serotonergic/Tryptamine/Indole	Plant
<i>Peyote, San Pedro, Huachuma</i>	mescaline	3,4,5-trimethoxyphenethylamine	Classic/Serotonergic/Phenethylamine	Plant
<i>Bufo</i>	Bufotenine	5-OH-DMT, 5-Hydroxy-N,N-dimethyltryptamine	Classic/Serotonergic/Tryptamine/Indole	Plant
<i>Yopo</i>	5-MeO-DMT	5-methoxy-dimethyltryptamine, derivative of 5-OH-DMT	Classic/Serotonergic/Tryptamine/Indole	Plant
<i>Psilocin</i>	4-HO-DMT	4-hydroxy-N,N-dimethyltryptamine	Classic/Serotonergic/Tryptamine/Indole	Fungi
<i>Psilocybin</i>	4-PO-DMT	O-Phosphoryl-4-hydroxy-N,N-dimethyltryptamine;	Classic/Serotonergic/Tryptamine/Indole	Fungi
<i>Ecstasy/MDMA</i>	MDMA	3,4-methylenedioxymethamphetamine	Atypical/Entactogen	Chemical
<i>Ketamine</i>	ketamine	C13H16ClNO	Atypical/Dissociative/NMDA receptor antagonist	Chemical
<i>Phencyclidine / PCP</i>	phencyclidine	CI-395, phenylcyclohexylpiperidine	Atypical/Dissociative/NMDA receptor antagonist	Chemical
<i>Ibogoids</i>	Ibogaine	ibogaine hydrochloride	Atypical/Dissociative/NMDA Agonist/Complex Tryptamine	Plant
<i>Cannabis</i>	THC +	tetrahydrocannabinol +	Atypical/Cannabinoid Agonist	Plant
<i>Scopolamine</i>	hyoscine	scopolamine	Atypical/Muscarinic receptor antagonist	Plant
<i>2C-family</i>	various	2,5-dimethoxy, 4-substituted phenethylamines	Atypical/Serotonergic/Phenethylamine	Chemical
<i>D0x family</i>	various	2,5-dimethoxy, 4-substituted amphetamines	Atypical/Substituted amphetamine derivative/5-HT agonist	Chemical
<i>NBOMe derivatives</i>	25I-NBOMe	2C-I-NBOMe, Cimbi-5	Atypical/derivative of the substituted phenethylamine	Chemical
<i>Harmaline</i>	Harmaline	C ₁₃ H ₁₄ N ₂ O	Beta-carboline/Indole/MAO inhibitor	Plant
<i>Fly Agaric Mushroom</i>	ibotenic acid, muscimol	Muscarine, muscazone	Muscarinic	Fungi

<i>Salvi Divinorum</i>	salvinorum a	salvinorin A, trans-neoclerodane diterpenoid	Diterpene	Plant
<i>Morning Glory Seeds</i>	lysergic acid amide (LSA)	lysergic acid amide (LSA)	Classic/Serotonergic/Tryptamine/Indole	Plant
<i>AMT</i>	aMT	α -Methyltryptamine	Tryptamine/ Entactogen	Chemical
<i>Tobacco / Nicotiana Rustica</i>	nicotine, beta-carbolines, harmala alkaloids	C ₁₀ H ₁₄ N ₂ , harmala alkaloids	Solanaceae, chiral alkaloid, source of MAOIs	Plant