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

October 2022

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Acknowledgements

This report was planned and written by Brian, Olivia, and Ron, with Brian as senior author and equal contributions from Olivia and Ron. Jonathan Ramirez conducted the Covidence literature search and organized the initial results for analysis. Our special thanks to Leann Cunningham, Nina Thompson, and Kaitlyn Rideout for their work on analysis and support in writing up parts of the report. Olivia Marcus was supported by NIDA grant (T32 DA007233); points of view are the authors alone. We also thank Eric Dumont, Associate Professor in the Department of Biomedical and Molecular Sciences School of Medicine Faculty of Health Sciences at Queen’s University, for his support. Ken Tupper generously conducted a meticulous and sophisticated peer-review, as well as an insightful expert commentary in the main report to orient the reader.

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Objectives

We embarked on a rapid but comprehensive 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. Specifically, we aimed 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.
- 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.
- Highlight gaps in knowledge and opportunities for research investment in the Canadian context.

Audience

This report is meant to broadly summarize the state of the research and other recent developments in psychedelic science in a way that is accessible for the curious practitioner, researcher, student, government agent, public health servant, or policymaker who wonder what is stimulating such statements as ‘we are experiencing a renaissance in psychedelic research’. The target audience for this report are those who want to learn more about who has studied what, the current hypotheses being tested or proposed, and what remains to be tested, questioned, and/or discussed among researchers, clinicians, policymakers, public health servants, guides, people with lived experience, and traditional and Indigenous communities.

Coverage

We aimed to educate key 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, safety, methodology and study design, and other considerations. We highlight studies that are focused on a broad range of health conditions with a broad methodological focus that includes surveys, clinical trials and naturalistic studies. In addition to these topics, we synthesized research and commentary on representation of research populations, regulation and policy, credentialing, issues related to Indigenous populations, and the role of psychedelics in overall population health and wellness. To conclude we offer our perspective on research gaps and provide a framework to support further discussion and prioritization among key stakeholders. The reader is referred to our main and summary reports for a thorough description of the scope and methodology of the literature search and review process.
Historical and Current Canadian Context

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, meant that they were considered as having a high potential for non-medical use\(^1\), no currently accepted therapeutic application, and a lack of accepted safety for use under medical supervision. The combination of the socio-political climate, shrinking funding opportunities, and methodological issues have severely limited new research and development since the 1970s.

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 and 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

\(^1\) 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”, all of which fall under the broad term “substance use health”.
between 2010-2020, marking an all-time high in 2020, which has likely been surpassed in the following years.

**Treatment Outcomes Related to Substance Use Disorders**

The general picture that emerges from the research on psychedelic-assisted treatment for substance use disorders is one of considerable promise. While research reviews call for more controlled trials, especially those that are well blinded and with sufficient sample size to detect clinically meaningful group differences, there is clearly sufficient evidence to warrant further investigation. This is especially true 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 opioid overdose epidemic. Promising and consistent results have come from some controlled studies, albeit with small samples and/or proof of concept designs: for psilocybin and tobacco use disorder; LSD and alcohol use disorder; and ketamine and cocaine use disorders, cannabis use disorders and opioid withdrawal, either alone or in combination with other therapeutic agents. Naturalistic observational studies with ayahuasca and cross-sectional research with healthy individuals in the community also lend important information to the promising picture. The largely underground work with ibogaine and opioid withdrawal is also worthy of focused attention and appears to hold promise, although any protocol for sanctioned research will have to include extensive screening and risk management procedures.

**Treatment Outcomes Related to Depressive Disorders**

As with substance use disorders, the current research evidence for depressive disorders is promising while also calling for considerably more research. Early and promising results for psilocybin and ayahuasca are particularly noteworthy. Psilocybin has been investigated 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 reductions of depressive symptomology for up to 24 weeks with sustained effects measured to six months. With respect to ketamine, by far the most studied psychedelic for depression, the results are quite inconclusive.

Given the high prevalence of depressive disorders, including treatment resistant depression, psychedelics may present as a safe, viable, effective, and novel form of treatment, which requires continued study and support. Currently, established therapeutic benefits always occur within a larger therapeutic framework, generally in the form of psychological support.
Treatment Outcomes Related to Anxiety Disorders Including PTSD

Apart from ketamine, MDMA is the most advanced of any psychedelic 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 powers of effect and a standardized, manualized approach to therapy.

High-dose ketamine in combination with structure therapy may be of benefit for people with treatment-resistant depression and PTSD. It 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 support. Ketamine has demonstrated both 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.

Psilocybin has proven beneficial in response to end-of-life distress. Psilocybin for end-of-life distress or cancer-related anxiety trials have been among the most methodologically sound and have good power of effect in reducing depressive and anxious feelings at end-of-life in a dose-dependent manner. Given the humanitarian responsibility to respond to suffering related to terminal diagnosis, and the fact that Canadians can already access Medical Assistance in Dying, it seems prudent to further explore the potential models and outcomes of psilocybin-assisted therapy at end-of-life.

Treatment related to Other Health and Mental Health-related Conditions

The main report also summarizes the clinical research on therapeutic potential of psychedelics for:

- Eating Disorders and Body Dysmorphic Disorders
- Headache and pain
- Anxiety and Social Connectedness in Autism Spectrum Disorder (ASD)
- Personality Disorders
- Schizophrenia
- Grief
• Alzheimer’s, Dementia, and Neurocognitive Disorders
• Traumatic Brain Injury

The reader is referred to the main report for a more detailed summary of trial results concerning each of these topic areas, some showing promise, others less so.

We also explored the relationship between psychedelic use and well-being, cognition, mindfulness, and creativity with the aim to balance the clinical research on signs and symptoms of mental illness or severe distress with the research that investigates activities and interventions aimed at improving or maintaining overall well-being, as well as preventing mental illness or cognitive decline in healthy individuals. While results vary somewhat by the psychedelic substance under investigation, participants in research often report increased satisfaction with life, non-judgement, awareness, improved mood, creativity, concentration, and cognition. Similar results are found in several large-scale population surveys, including associations with reduced use of alcohol and other drugs, reduced indices of psychopathology, psychological distress, and suicidality.

Microdosing

The microdosing literature remains early and exploratory, with clear limitations on existing study designs such as lack of randomized placebo-controlled trials. Preliminary findings do, however, support the exploration of the safety and therapeutic efficacy of microdosing psychedelics for depression and experts recommend that future trials should consider added blinding mechanisms to reduce expectancy bias, as well as comparative studies between people with psychedelic experiences and those without. Research on microdosing may also be best served by clarifying and defining the range of dosages (i.e., microdose, very low dose, low dose) for each psychedelic compound and recognizing the many factors known to modulate therapeutic drug effect, including belief, trust in the modality, setting, and cultural beliefs.

Research and Regulatory Considerations

The main report covers a wide range of topics related to research and regulatory processes, each of which are challenging to summarize in this brief overview of the research synthesis.

Safety

The main report offers considerable detail on safety concerns specific to psilocybin, ayahuasca, MDMA, ketamine, and igoba/igobaine. We also provide a brief discussion on the topic of therapist abuse and patient safety in light of 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 female) to limit patient vulnerability (Passie, 2018). 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.

**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). Psychological supports provided in clinical psychedelic research settings remain an important factor for interpreting study findings.

The main report offers gaps and opportunities for clinical trial design. Assessments of clinical trials evaluating psychedelics show wide variation in study design, limited follow-up periods and small, non-representative samples, all challenging interpretation of the results. Careful, large-scale, multi-site and placebo-controlled RCTs are needed to clarify the empirical status for specific clinical conditions such as depression, as well as for more experimental trials on healthy volunteers. Greater diversity in study participants would increase generalizability and larger trials would improve statistical power.

**The Importance of Mixed Methods and Naturalistic Design**

This section of the main report addresses the salience of diversity in methodology and study design in investigations with psychedelics, particularly those classed as entheogens and used in ritual-ceremonial contexts. 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. 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).

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2 We recognize the limitation of a binary gendered approach and encourage more gender-diverse or nonbinary frameworks in thinking about therapeutic dyads.
Diversity/Equity Representation in Current Research

The so-called renaissance of psychedelic medicine has stimulated a great deal of excitement, yet it also is challenging for many skeptics who are hyperaware of the historical patterns of erasure and inequity when it comes to political and technological (i.e., medical) innovations. Some authors have drawn attention to the question of equity in psychedelic-assisted therapies in the Global North, particularly concerning lack of inclusion of people of color 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 communities. Importantly, 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. BIPOC communities also need to have their voices heard as psychedelic research expands.

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. Many classic psychedelics such as *Psilocybe* mushrooms, ayahuasca, peyote, *huachuma*, *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.

Role and Rights of Indigenous Peoples

This section of the report discusses the role of Indigenous peoples, their autonomy, and Indigenous methodologies for research and healing. In brief, it has been established under the 2007 United Nations Declaration on the Rights of Indigenous Peoples (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 principles of good practice. Further, Indigenous peoples have used a wide range of psychoactive plants for millennia in a ritualistic context that emphasized community wellbeing, healing, rites of passage, spirituality and which also provide a context for safe usage. 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.
A Public Health Perspective: Prevention, Health Promotion and Healthy Drug Policy

Studies of psychedelic use in the general population show promising associations with general well-being, but further population-level research is needed to fully establish the balance of public good versus risk in increasing access to psychedelics.

Haden et al. (2016) had previously offered a “framework for the regulation and management of psychedelics based on public health principles”. The re-positioning of psychedelics as compounds of potential clinical benefit requires large-scale regulatory reform of current Canadian drug policy, but this reform possibility is not without precedent. The previous medical cannabis regulatory framework may prove a good fit for therapeutic access to psilocybin as decided between a medical practitioner and patient, and to allow for the expansion of further research and ease of restrictions for researchers.

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, and included 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.

Barriers to research include lack of funding for psychedelic 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. Progress is being made, however, with recent funding announcements from the Canadian Institutes for Health Research. Further research is also required understanding the current knowledge, attitude and behaviours of health care practitioners and policymakers pertaining to psychedelics and psychedelic-assisted therapies as well as the evaluation of practitioner training programs.

Training and Certification

The main report considers the role of training, harm reduction, clinical competencies, an independent credentialing council to regulate and credential practitioners, as well as the adoption of a Code of Ethics among psychedelic-assisted therapy practitioners. 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-therapies are to be fully investigated. In addition, as noted above, there is a need to
evaluate different training curricula and processes for professionals aiming to work within a particular scope of practice.

Research Gaps and Implications for Funding

This rapid review of the therapeutic application of psychedelics reveals a vast, but uneven and still emergent body of knowledge. Psychedelics are presenting as a novel and promising treatment for a wide range of clinical and psychiatric conditions, suggesting some shared underlying mechanism of change, which may help identify common or unified bases between apparently separate conditions.

The clinical research on classical and atypical psychedelics warrant the following:

- Additional trials to confirm therapeutic dose, optimal number of doses, and the relative contributions of the psychological supports and complementary therapies provided.
- Trials of group therapy settings and collective ceremonial ritual, including within neo-shamanic or ayahuasca church settings.
- Trials using natural compounds or naturally extracted compounds are also largely missing from the literature. Investigations into compounds that are directly derived from natural sources may reveal additional benefit, possibly due to entourage effect.
- Address issues of small sample sizes; lack of placebo; difficulties in blinding the psychedelic effect; expectancy bias; homogenous research sample populations and heterogeneous trial designs.
- Address the fundamental synergistic effect of pharmacotherapies with psychotherapy or other psychological support. This includes inquiry into the various psychedelic-assisted therapy models, especially in MDMA for PTSD, given the high-cost and time commitments of the currently researched MAPS-sponsored manualized therapy for PTSD.
- Population health research to monitor benefits and risks associated with increasing use of psychedelics
- Knowledge synthesis as well as knowledge exchange and transfer are critical to the development of accurate public information regarding psychedelics. Lower risk use guidelines as exist for alcohol and cannabis can be replicated for psychedelics, ensuring public safety, and minimizing risks and harms.
Framework to Support Research Prioritization and Future Consultation

Given the complexity of the field and 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. Prioritizing among health conditions could consider burden of disease and 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 the BIPOC population, 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 taking into account factors such as workforce capacity with required competencies, relative cost-effectiveness and equity considerations with respect to eventual access of evidence-based interventions.

**Figure 1. A Framework for Identifying and Prioritizing Research Gaps and Opportunities**

In Table 1, we suggest a starting place for future conversation based on an overall assessment of the potential considerations identified above in the 2 x 2 framework. Of course, the real challenge will be drilling down on the various possibilities. To support that process we suggest starting with health conditions and psychedelic substance and then drilling down from there based on population group and type of treatment model or intervention.
### Table 1. Suggested priority areas within the four domains

<table>
<thead>
<tr>
<th>Suggestions for prioritizing within health condition</th>
<th>Suggestions for prioritizing by psychedelic substance</th>
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</thead>
<tbody>
<tr>
<td>- Substance use disorders</td>
<td>- MDMA</td>
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<tr>
<td>- Depressive and anxiety disorders</td>
<td>- Psilocybin</td>
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<tr>
<td>- Mood</td>
<td>- Ketamine</td>
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<td>- PTSD</td>
<td>- Ayahuasca</td>
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<td>- End of life distress</td>
<td>- Ibogaine</td>
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<td>- OCD</td>
<td>- 5 MEO DMT</td>
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<td>- Eating disorders/BDD</td>
<td>- Mescaline/peyote</td>
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<td>- Neurological/organic</td>
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<td>- Pain and headache</td>
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<td>- Stroke recovery</td>
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<table>
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<tr>
<th>Suggestions for prioritizing within population sub-groups</th>
<th>Suggestions for prioritizing within treatment models and interventions</th>
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</thead>
<tbody>
<tr>
<td>- Women and gender issues</td>
<td>- Alternative approaches for psychedelic-assisted therapy including ritualistic models</td>
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<tr>
<td>- Age including youth and older adults</td>
<td>- Post-intervention integration strategies</td>
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<tr>
<td>- BIPOC, including Indigenous People and other marginalized (e.g., homeless)</td>
<td>- Therapist assisted</td>
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<td>- Veterans, First Responders and Health Care Workers</td>
<td>- Peer and family-support</td>
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<td>- Virtual</td>
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<td></td>
<td>- Mixed treatment models (e.g., combining with neurofeedback, mindfulness, Acceptance and Commitment therapy)</td>
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<td></td>
<td>- Evaluation of training and certification</td>
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### 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.
Conclusion and Next Steps

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 certainly more robust discussion.

There is every indication that research in this area will continue to accelerate on a Canadian and global scale. This highlights the need for enhanced research around a common agenda. There is also a need for ongoing research synthesis and knowledge translation activities that would engage diverse stakeholders, inclusive of clinicians, policy makers, Indigenous peoples and people with lived and living experience so as to maximize the relevance of the research questions being addressed as well as rapid translation of the ensuing research evidence to both healthy policy and practice.