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Expanded access to psychedelic treatments: comparing American and Canadian policies

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The United States Food and Drug Administration's (FDA's) August 2024 determination that an additional phase III study will be required to consider the approval of midomafetamine for the treatment of post-traumatic stress disorder (PTSD) could delay the potential approval of this promising treatment by several years.[1] In principle, the FDA's expanded access pathway could enable broader access to investigational treatments as clinical trials continue. However, this alternative pathway is so burdensome that few patients are likely to benefit. Adoption of elements based on the Canadian model to expanded access may help more patients gain access to psychedelic therapy while simultaneously providing data about safety and efficacy for the FDA to consider in future reviews of these treatment approaches.

In January 2022, Health Canada instituted regulatory amendments to include 3-[2-(dimethylamino)ethyl]-4-phosphoryloxy indole (psilocybin) and *N*-methyl-3,4-methylenedioxyamphetamine (MDMA) as drugs that can be requested as part of the special access program (SAP). The SAP is designed to support licensed healthcare practitioners who are seeking treatment options for patients with a serious or life-threatening condition where conventional treatments have either failed, are unsuitable or are not available in the country. In order to submit a request, an SAP form must be completed on a case-by-case basis, providing details on the patient's diagnostic history, previous treatment attempts (typically involving pharmacotherapies and non-pharmacological therapies) and scientific references indicating sufficient evidence of safety and efficacy to support the requested use. Currently, conditions explicitly named by Health Canada as falling within the scope of the SAP involving psychedelic-assisted therapy include end-of-life distress and treatment-resistant major depressive disorder (for psilocybin) and PTSD (for MDMA). Mandatory follow-up forms monitoring treatment response and serious and/or unexpected adverse reactions are required by Health Canada after drug administration.

In February 2024, 176 Canadians were authorised to access psilocybin via the SAP, with Health Canada approving 78% of applications for the drug.[2] Comparatively, 41 authorised requests were granted for MDMA.[3] Due to the difficulties associated with accessing MDMA as a treatment option for PTSD via the SAP (predominantly due to difficulties procuring pharmaceutical-grade MDMA), the Canadian Senate's Subcommittee on Veterans Affairs has advocated for a large-scale research programme on psychedelic-assisted psychotherapy to help expand the range of available treatment options for the 10% to 15% of Canadian veterans diagnosed with PTSD experiencing significant psychological distress and severe functional impairment.[4] Beyond veterans, it is also important to acknowledge that the number of civilian refugees and asylum seekers due to armed conflicts is increasing on a global scale, with estimates indicating a pooled prevalence rate of 23.70% for PTSD among those living in war-afflicted areas.[5] The increasing public health burden of PTSD[6] calls attention to the need to develop and expand access to evidence-based interventions including novel pharmacologically assisted psychosocial interventions for the treatment of PTSD.[7]

In the United States of America (USA), the FDA has a similar programme to Health Canada's SAP, known as expanded access, which serves as a potential pathway for patients with a serious or life-threatening condition to gain access to an investigational treatment outside of clinical trials when there is no comparable or satisfactory alternative therapy. Expanded access was first granted for MDMA in January 2020 as sponsored by Lykos Therapeutics (previously Multidisciplinary Association for Psychedelic Studies)

as part of the FDA's efforts to facilitate the development of this potential new medicine that the agency had designated as a breakthrough therapy. This application of the expanded access pathway allowed the drug to be administered to a total of up to 50 patients with PTSD at 10 qualified treatment sites.[8] Based on available records, expanded access for MDMA via Lykos Therapeutics was available from November 2021 to August 2023. To the author's knowledge, complete data on the safety and efficacy of this expanded access programme have not been made publicly available. As a potential proxy, available data based on the randomised, placebo-controlled phase III trial of MDMA-assisted therapy by the same sponsor indicated that in an ethno-racially diverse sample of 104 participants with PTSD (71.15% female, Mean age=39.08 (standard deviation (SD)=10.38)), 71.2% of participants in the MDMA group no longer met diagnostic criteria for PTSD post-treatment compared with 47.6% in the placebo group.[9] However, both mild and severe, but no serious (ie, life-threatening), treatment-emergent adverse events were noted as part of the study, including muscle tightness, nausea and decreased appetite, as well as suicidal ideation, insomnia and anxiety. These findings highlight the importance of physiological and psychological safety monitoring by present staff during sessions and systematic post-session monitoring in the weeks and months following treatment, especially in the context of expanded access. This will enable the continued documentation of adverse events on the part of patients accessing treatment via this expanded access pathway and facilitate appropriate intervention if necessary.

We are not aware of other expanded access approvals for MDMA, psilocybin or other psychedelic therapies in development despite the provisions granted to access experimental therapies via the Right to Try Act which allows eligible patients to access investigational drugs outside the context of clinical trials if they have exhausted all other approved treatment options. Broader application of the expanded access pathway to individual patients as well as cohorts of patients in clinical trials under umbrella applications (as was granted to Lykos Therapeutics) has the potential to contribute to the health of patients while providing supplementary sources of evidence for safety and efficacy. However, our discussions with investigators participating in the development of psychedelic medicine suggest this will not happen without efforts by the FDA to encourage and streamline the expanded access application process.

Comparing the Canadian and American contexts regarding the accessibility of psychedelic treatments for serious health conditions, a few observations should be noted:

In the first 2 years of the SAP in Canada, over 200 patients were granted access to either psilocybin or MDMA with no serious adverse events being reported by Health Canada authorities. Preliminary data among a small segment of SAP patients (n=8, 50% female, Mean age=52.3 years (SD=10.7)) who received psilocybin treatment for cancer-related existential distress demonstrated significant improvements in anxiety, depression, pain, quality of life and spiritual well-being 2 weeks post-treatment.[10] No serious adverse effects were noted outside of common transient side effects including nausea/vomiting (4/5), headache (3/5), sweats/chills (3/5) and crying (3/5). The benefits experienced by SAP patients are consistent with clinical trial data, with multiple studies showing significant and persisting reductions in depression and anxiety after high-dose psilocybin administration in patients with cancer-related psychosocial distress.[11] Moreover, the limited adverse events reported in Canada appear to be consistent with meta-analytic findings indicating that classic psychedelics such as psilocybin are generally well tolerated in clinical settings.[12] At present, the SAP continues to provide access to psilocybin or MDMA to patients who have been unresponsive to available treatments. Moreover, the range of conditions within the SAP scope of the approval is actively expanding (eg, access to psilocybin for cluster headache was granted in June 2024).[13]

In contrast, only 50 patients have had access to MDMA in the USA via the FDA's expanded access pathway from the initial approval of MDMA for PTSD in 2020 to the present day. Access was only granted to 10 approved sites, greatly limiting access to individuals living outside of California (3 sites), Colorado (1 site), Connecticut (1 site), Maine (1 site), Maryland (1 site), New Mexico (1 site), North Carolina (1 site) and Oregon (1 site). Moreover, with a population of over 340 million compared with Canada's 41 million, the fact that Canada has already provided services to more than four times the number of patients in the USA in half the time raises questions of equitable access to care and the restrictions to the controlled and closely monitored medical use of these drugs by qualified and licensed healthcare practitioners.

As basic principles of biomedical ethics,[14] value-based reasoning employing principles of justice, non-maleficence, beneficence and autonomy are crucial and are included by the United States Congressional Psychedelics Advancing Therapies caucus issues summary.[15] These values should be considered in the future of Health Canada's SAP and FDA's expanded access. Limiting access to care for patients who have exhausted all other treatment options and may not qualify for participation in a clinical trial (with the added risk of not receiving the drug in the context of placebo-controlled trials) may indeed violate these principles. Specifically, care should be granted in a non-arbitrary and consistent manner (justice) to patients who can decide and provide informed consent to access care (autonomy), to a treatment that has sufficient empirical data (beneficence), while safety and effectiveness are closely monitored by a qualified treatment team and federal regulators (non-maleficence). Health Canada's SAP, although not without limitation, appears to be more in line with these principles. The FDA's expanded access pathway appears to present greater institutional barriers to open, ongoing and equitable access to psychedelic treatments, resulting in the present-day absence of available treatment options to patients that is not without consequence. In addition to the distress and impairment associated with depression and PTSD, when symptoms are unremitting across years, the risk of adverse health outcomes and mortality is increased.[16 17]

Taken together, and in light of ongoing reform surrounding psychedelic treatments, the available evidence suggests that greater consideration should be given to the accessibility of psychedelic therapies under the FDA's expanded access pathway, with an emphasis on increasing transparency, public and professional awareness, and ultimately, the utilisation of this pathway by patient populations with a demonstrated need for alternative treatment options.

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