Psilocybin mushrooms for psychological and existential distress

Treatment for a patient with palliative lung cancer

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Psychedelic medicine is currently undergoing a renaissance, with interest in the medical use of these compounds exploding after decades of dormancy.[1] This has occurred primarily under the purview of medical researchers; however, recent legal precedents in Canada have allowed some access to psilocybin (the psychedelic compound found in *magic mushrooms*) for front-line clinicians and their patients.

Here we describe the case of a woman with advanced lung cancer and substantial existential and psychological distress who was treated with psilocybin-assisted therapy by family physicians in a rural community setting. Consistent with the use of psilocybin in clinical trials, the 1 psilocybin session occasioned an experience of a *mystical* nature that the patient would later describe as the single-most personally meaningful experience of her life. This experience led to immediate, substantial, and sustained improvements in her distress and quality of life.

Case

A 54-year-old woman from rural northern Ontario with stage IV small cell lung cancer presented with severe anxiety and depression regarding her palliative diagnosis. Despite feeling well physically, she described her quality of life as poor. She was anxious about her impending death, felt powerless, and questioned the meaning of her life. She had previously tried and not benefited from escitalopram, sertraline, and counseling. Through the Internet she had learned

Editor's key points

- In August 2020 Health Canada granted patients with life-threatening diagnoses and existential and psychological distress legal access to psilocybin-containing mushrooms, making psilocybin legally accessible outside of clinical trials for the first time since 1974. Health Canada is currently granting legal access on a case-by-case basis through the Special Access Program.
- Two small randomized controlled trials have demonstrated that a single psilocybin session combined with psychotherapy leads to immediate, substantial, and sustained improvement in psychological and existential distress in those with life-threatening cancer.
- Patients in Canada may ask doctors to support their requests for legal access to psilocybin, which puts physicians in an unusual position given that psilocybin is not yet approved as a treatment by either Health Canada or the United States Food and Drug Administration.
- If a physician is interested in supporting a patient in their request for access but does not have training or clinical experience in psychedelic medicine, then referral to an expert should be considered.

Points de repère du rédacteur

- En août 2020, Santé Canada a accordé à des patients ayant reçu un diagnostic de maladie mortelle, et de détresse psychologique et existentielle le droit d'accéder légalement à des champignons contenant de la psilocybine, rendant la psilocybine légalement accessible en dehors des essais cliniques pour la première fois depuis 1974. À l'heure actuelle, Santé Canada autorise cet accès légal au cas par cas, par l'entremise du Programme d'accès spécial.
- Deux petits essais randomisés contrôlés ont démontré qu'une seule séance d'administration de psilocybine, combinée à une psychothérapie, a entraîné une amélioration immédiate, considérable et soutenue dans la détresse psychologique et existentielle de personnes atteintes d'un cancer mortel.
- Des patients au Canada peuvent donc demander à leur médecin de donner son appui à leur demande d'accès légal à la psilocybine, ce qui place le médecin dans une position inusitée, puisque ni Santé Canada ni la Food and Drug Administration des États-Unis n'a encore donné son approbation à la psilocybine comme traitement.
- Si un médecin considère la possibilité de cautionner un patient dans sa demande d'accès, mais qu'il n'a pas de formation ou d'expérience clinique en médecine psychédélique, il y aurait lieu d'envisager un aiguillage vers un expert.

about a Canadian woman with a palliative diagnosis and similar symptoms who had reported dramatic improvement from legal psilocybin-assisted therapy.

Interested in psilocybin herself, the patient contacted a rural generalist physician (R.P.M.) in her region who had formal training and clinical experience with psychedelic medicine (subanesthetic ketamine). He conducted a thorough psychedelic medicine assessment and obtained ongoing consultation and mentorship from experts in urban southern Ontario. Consistent with selection criteria used in psilocybin clinical trials, the patient was not taking an antidepressant, had no brain metastases, and had no personal or family history of psychosis. She had a strong support network and had not experienced childhood trauma. She had no previous psychedelic experience.

The family physician then wrote a support letter and submitted it to Health Canada. Ten business days later the patient was granted a section 56(1) exemption to the Controlled Drugs and Substances Act (CDSA), allowing her to legally possess and consume psilocybin mushrooms.

The process for treatment with psychedelic medicine was then initiated, which consisted of preparation, a psilocybin dosing session, and integration. Consistent with protocols employed in clinical trials, the male-female therapist dyad (in this case, 2 rural family physicians [R.P.M. and S.T.]) spent a total of 8 hours preparing the patient for the psilocybin session.[2-4] Preparation was aimed at optimizing *set* and *setting*, including cultivating an open mindset in the patient regarding expectations and intentions as well as preparing a comfortable setting in which the psychedelic experience could unfold (physical and social environments). Supportive practices including meditation and time in nature were encouraged. Risks and benefits were discussed based on the information available in the scientific literature, and informed consent was obtained.

Approximately 2 to 3 weeks before her formal dosing session, without consulting or informing her health care team, the patient took a small amount of mushrooms on her own (approximately 1.5 g dried mushrooms, or about 30% of the full dose planned for the dosing session). She reported that this experience was scary for her and almost led to her canceling the dosing session. However, over the ensuing 1 to 2 weeks she felt lighter and reported that the experience was therapeutic and unburdening. Her interest in the full-dose therapeutic session was renewed and she consented to proceed.

The formal dosing session was then conducted in a living room–like environment under the supervision of the therapist dyad. The patient consumed 5 g of dried psilocybin mushrooms as a tea and was directed to go inward as she laid down with eye shades on and headphones playing gentle, guiding music. A quantity of 5 g was selected to approximate the dose of psilocybin used in clinical trials, based on reports of psilocybin concentrations in the *Psilocybe cubensis* mushrooms that she was to consume.[3,5] Approximately 90 minutes after consuming the mushrooms, the patient burst into tears, which she described as "tears of healing." She said she had encountered a "great mystery" or "sentient being" that was incredibly comforting but difficult to describe with words. The effects of the psilocybin had worn off completely after 4 to 5 hours. Her psilocybin mushroom experience met medical criteria for a *complete mystical experience* based on the Mystical Experience Questionnaire–30 (**Figure 1**).[6]

Follow-up sessions focused on the patient integrating what she had experienced into day-to-day life. They were conducted the following morning, 1 week later, and monthly thereafter. She completed validated questionnaires (General Anxiety Disorder–7 questionnaire, Patient Health Questionnaire–9, and McGill Quality of Life Questionnaire–Revised) that showed marked improvement in her mood, anxiety, and quality of life, including psychological, existential, and social subscales (**Figures 2** and **3**). These results were sustained at 4 months, at which time the patient rated the experience using the Persisting Effects Questionnaire as the single-most "personally meaningful," "psychologically insightful," and "psychologically challenging" experience of her life. She said the experience served as a daily "spiritual anchor" for her during her cancer journey, allowing ongoing and ready access to that space in her consciousness where she felt present, connected, joyous, and free.

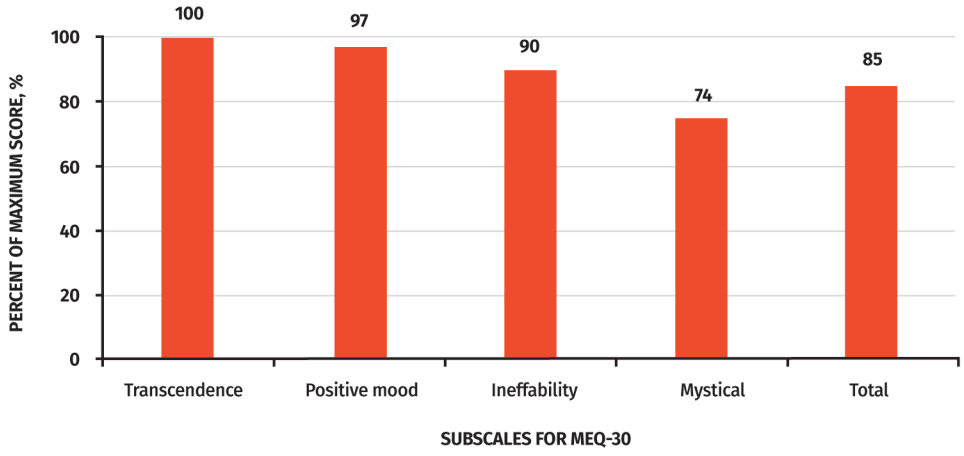
Discussion

In August 2020, 4 Canadians with life-threatening diagnoses became the first to be approved by Health Canada for legal access to psilocybin mushrooms to address psychological and existential distress. This was the first time since 1974, when psilocybin was placed on Schedule III of the CDSA, that psilocybin had been legally accessible to anyone in Canada outside clinical trials.

Recent medical interest in psychedelic compounds such as psilocybin is not new. In the 1950s and 1960s more than 1000 clinical papers were published on psychedelics, including more than 40,000 patients treated.[7] Psychedelics were then made illegal in the early 1970s as a consequence of political forces—not owing to a lack of promising results or scientific interest—and research came to a halt.[8]

After decades of quiescence, medical research into psychedelics resumed in the 1990s and early 2000s. In 2011 a small study was published assessing psilocybin for the treatment of anxiety in patients with advanced-stage cancer.[9] This pilot study (N=12) was followed in 2016 by the publication of 2 well-designed randomized controlled

Figure 1. Patient's MEQ-30 scores after high-dose psilocybin mushroom session: *Two days after her high-dose psilocybin experience the patient completed the MEQ-30, a validated tool to assess mystical experiences, with the degree of mystical experience appearing to mediate clinical outcomes. The patient had a "complete" mystical experience, as defined by a score of ≥60% in each of the categories of mystical experience.*



MEQ-30—Mystical Experience Questionnaire (30 questions).

trials (RCTs) by researchers at Johns Hopkins University in Baltimore, MD (N=51), and at New York University, NY (N=29).[3,4] These studies assessed patients with life-threatening cancers for a number of clinical outcomes including *existential distress*, which has been defined as mental distress experienced by those facing imminent death and includes death anxiety, loss of meaning or purpose, powerlessness, and fundamental aloneness.[10]

Both RCTs employed a double-crossover design and concluded that a single session with high-dose psilocybin, when combined with preparatory and integrative psychotherapy, led to immediate, substantial, and sustained improvement in psychological and existential distress as well as improvements in quality of life.[3,4] In the Griffiths et al RCT, the Cohen *d* effect size on the primary outcome (GRID-Hamilton Depression Rating Scale–17 for depression) was 2.98 at 6 months.[3] In the Ross et al RCT, the Cohen *d* effect size on the primary outcome (Hamilton Depression Rating Scale total for cancer-related depression and anxiety) was 1.36 at 7 weeks after the dosing session.[4] Effects lasted to study completion, which ranged from 6 months in the original studies to more than 4 years in a follow-up study.[11] A secondary analysis also showed reductions in suicidal ideation and loss of meaning that were sustained to 6.5 months and 4.5 years, respectively.[12]

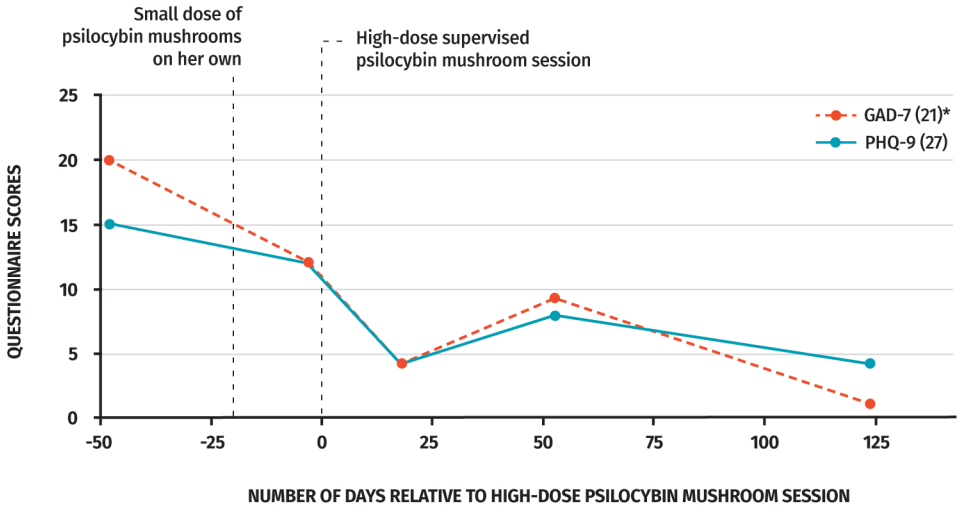
No serious adverse events occurred in either RCT. Side effects were transient and included moderate increases in systolic and diastolic blood pressure, nausea and vomiting, headache, and some mild physical and psychological distress that all resolved without intervention. No participants abused or became addicted to psilocybin and there were no cases of prolonged psychosis or hallucinogen persisting perceptual disorder.[3,4]

Interestingly, both RCTs reported that clinical outcomes appeared to be mediated by the degree of mystical-type experience reported by the patient, which has been defined as direct experience of unity, transcendence of time and space, sacredness, deeply felt positive mood, ineffability, and a sense of encountering ultimate truth or reality.[3,4,13] Sometimes also called spiritual or religious experiences, a critical defining feature is the feeling of becoming one with all that exists. These experiences are often rated as being one of the most spiritually or personally meaningful experience of one's life and are associated with immediate, substantial, and sustained changes in one's behaviour and perceptions.[14]

While the results of these psilocybin clinical trials are promising and supported by a systematic review and meta-analysis published in 2021,[15] psilocybin is still an investigational substance and is not currently approved for any medical indication. Health Canada has stated that Canadians seeking legal access to psilocybin have 3 potential pathways[16]:

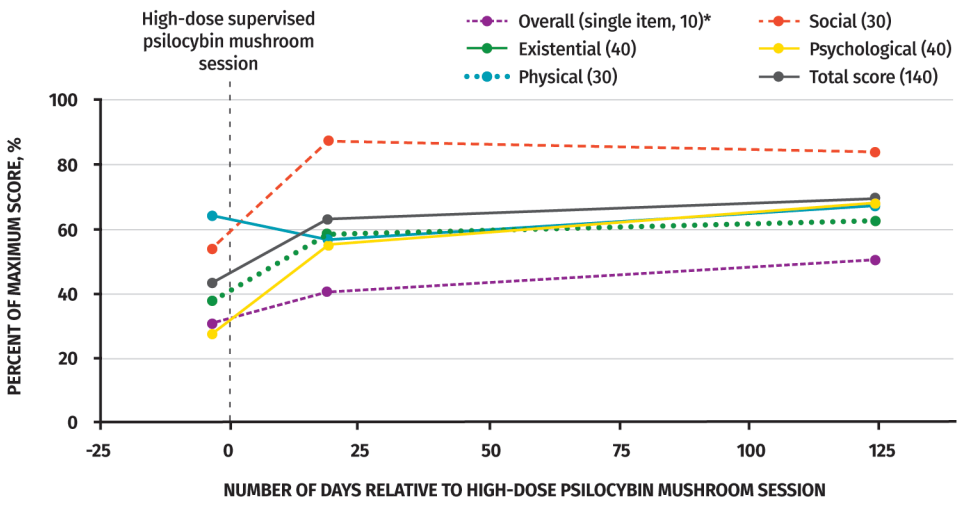
Clinical trials. In a recent announcement about psilocybin, Health Canada stated that clinical trials are the best method to advance research on unproven drugs as they protect participants and "help build the evidence related to the safety and efficacy of treatment options."[17]

Figure 2. Patient's depression and anxiety scores before and after the high-dose psilocybin mushroom session: *Depression and anxiety scores are shown from the time of initial assessment to follow-up 4 months after the patient's high-dose psilocybin session. Notably, the patient took approximately 1.5 g of dried psilocybin mushrooms several weeks before the high-dose (5 g) session, without telling her medical team at the time; however, she said her anxiety and depression improved, which is supported by her scores. At initial presentation, her scores fell in the severe anxiety and moderately severe depression categories. Four months after her high-dose session, her scores did not even reach criteria for mild depression or anxiety. The spike at day 53 coincided with a pneumonia and an associated, transient worsening of her physical health.*



GAD-7—General Anxiety Disorder–7 questionnaire, PHQ-9—Patient Health Questionnaire–9.
*Maximum scores of questionnaires shown in brackets.

Figure 3. Patient's quality-of-life scores before and after the high-dose psilocybin mushroom session: *Quality-of-life scores are based on the MQOL-R, a validated tool for those with life-threatening illnesses that has 4 subscales (existential, physical, psychological, social). Improvement was observed in 3 subscales (existential, psychological, social) 18 days after the high-dose psilocybin session; results were sustained to follow-up 4 months later. No changes were noted in the physical subscale.*



MQOL-R—McGill Quality of Life Questionnaire–Revised
*Maximum scores shown in brackets.

Notable challenges for patients in accessing clinical trials for psilocybin include the scarcity of clinical trials, potentially strict inclusion and exclusion criteria, the timeframe to undergo screening and protocols for someone who may have limited life expectancy, and geographic barriers for rural patients who would have to travel to urban research centres to participate.

Special Access Program (SAP). Meant to allow Canadians access to promising drugs from phase 2 and 3 clinical trials that have not yet completed regulatory approval in Canada, including chemotherapeutic agents, SAP was expanded in January 2022 to restore access to previously restricted drugs such as psilocybin.[18] The SAP route requires a prescriber to complete an online application and then connect with a licensed dealer who can supply synthetic psilocybin that complies with good manufacturing practices. The prescriber must then receive the psilocybin and follow strict storage, handling, documentation, and reporting practices. Approvals for psilocybin have been granted using the SAP route for patients with life-threatening illness.[19]

Section 56(1) exemption to CDSA. While this form of access is still listed as an option, Health Canada states preferred routes are through clinical trials or SAP.[16] Since January 2022, patients who have applied through section 56 exemptions have had requests denied and been told they should pursue other "existing legal routes," such as clinical trials or SAP (Health Canada response to patient application; February 22, 2022).

The SAP may be the only practical route for legal access at the time of this article, given the barriers to enrolling in clinical trials and Health Canada denying section 56(1) exemption requests; however, patient advocacy groups have reported that the SAP process is onerous for prescribers and there is a lack of family doctors who are willing to complete the application (personal communication with TheraPsil; June 30, 2022).

There are now numerous institutions in Canada offering psychedelic therapy training for interested family physicians. In the interim, if you are aware of a patient with a life-threatening diagnosis who may benefit from psilocybin, consider referring them to a physician with expertise in psychedelic therapy. Given that the number of health care providers with training in this emerging area is limited, clinicians are welcome to contact the authors of this article for more specific information.

Conclusion

Our case presentation describes one of the first people in Canada to legally receive psilocybin mushrooms for existential and psychological distress at end of life. The family physician team had previous training and clinical experience with both psychedelic medicine and palliative care and adapted the approach used in clinical trials to care in a rural community setting. Substantial attention was paid to the preparation of the patient beforehand and integration afterward. While psilocybin is still an investigational intervention, this patient responded as RCTs have suggested, with the 1 psilocybin mushroom session occasioning a mystical-type experience that she rated 4 months later as being the single-most personally meaningful experience of her life. This was associated with immediate, substantial, and sustained improvement in her psychological and existential distress and in her quality of life.

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Competing interests

Dr Emma Hapke is paid for her work as Principal Investigator of a phase 3 study of 3,4-methylenedioxymethamphetamine–assisted psychotherapy for posttraumatic stress disorder (Montréal site), sponsored by the Multidisciplinary Association of Psychedelic Studies, and serves as paid Associate Director of the Nikean Psychedelic Psychotherapy Research Centre, a nonprofit academic research centre based at the University Health Network in Toronto, Ont. **Dr Sean O'Sullivan** previously served as paid medical director and board member of TheraPsil, a nonprofit advocacy organization whose purpose is to legalize psilocybin therapy for Canadians with terminal diagnoses and other conditions. **Dr Hapke** previously served as a volunteer board member of TheraPsil, and **Dr Ryan Patchett-Marble** was previously a volunteer clinical adviser for TheraPsil.

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