Australian Government
Department of Health

Application to Amend the Poisons Standard to Expand the Restricted Medical Use of Psilocybin to Include Existential Distress Towards End-of-Life.

7th March 2025

Palliative Care Psychedelic-Assisted Therapy Coalition

The Palliative Care PAT Coalition is a group of healthcare professionals advocating for the responsible use of psychedelic-assisted therapy in palliative care to improve quality of life. We envision a future where patients can access the best healthcare, free from the stigma surrounding psychedelics.

Members of the Palliative Care PAT Coalition include Ms Justine Topfer who works as a death doula in NSW; Dr Lauren Macdonald, a psychiatry doctor, psychedelic therapy guide and survivor of stage IV melanoma; Dr Janelle Trees, an Aboriginal rural and remote GP with specialist training and experience in palliative care; Shanae O'Leary, a Registered Psychologist with a clinical focus on trauma and research into psilocybin therapy for end-of-life existential distress; and Scott Edwards, Executive Officer at Mind Medicine Australia.

6 March 2025

The Secretariat
Medicines Scheduling Unit
Therapeutic Goods Administration
Canberra, ACT

Dear Sir/Madam,

Application to Amend the Poisons Standard by Retaining Psilocybine in Schedule 9 But Also Expending a Schedule 8 Entry to Include Access to Patients with Existential Distress at End of Life.

I am writing on behalf of Palliative Care Psychedelic-Assisted Therapy Coalition, with the support of Mind Medicine Australia, to respectfully request that the Therapeutic Goods Administration (TGA) expand the indications for psilocybin under the Poisons Standard to include patients with life-limiting illnesses who are suffering from severe existential distress. We believe that, under strict controls, psilocybin-assisted therapy should be an accessible option in palliative care settings, offering a compassionate and evidence-based response to profound end-of-life suffering.

We are attaching our application to request the expansion of psilocybin as a Schedule 8 controlled medicine when used as part of psychotherapy in medically controlled environments for terminally ill patients experiencing existential distress.

Over the past decade, numerous high-quality clinical trials have demonstrated psilocybin's strong safety and efficacy profile, particularly in alleviating anxiety, demoralisation and existential despair among patients nearing the end of life. Notably, multiple international trials (e.g., NYU, Johns Hopkins, UCLA) have shown rapid and sustained reductions in depression and anxiety in individuals with terminal diagnoses. The Swiss experience since 2014 confirms that palliative care specialists and psychiatrists have successfully integrated psilocybin therapy under controlled frameworks to alleviate end-of-life psychological distress. This accumulated data underscores the urgent need to make psilocybin-assisted therapy available to Australians facing life-limiting illnesses.

Psilocybin therapy aligns with the fundamental goals of palliative care: to relieve suffering, enhance quality of life, and respect patient autonomy. Just as our society has come to accept Voluntary Assisted Dying (VAD) as a choice for patients experiencing intractable end-of-life suffering, so too should patients have the option of psilocybin-assisted therapy if they are enduring existential distress. Denying such an option, particularly given the robust safety and efficacy evidence, would run counter to our commitment to patient-centred care.

We emphasise that psilocybin-assisted therapy would be strictly optional, no patient would be required to participate unless they and their treating specialist deem it appropriate. Undertaken only with fully informed patient consent, this ensures that patients understand the potential benefits, risks, and nature of the therapy before electing to proceed. Available only to those assessed as having the capacity to consent, thus ensuring ethical standards are upheld for vulnerable populations.

In preparing this application, the Palliative Psychedelic-Assisted Therapy Coalition and Mind Medicine Australia have taken into account:

i) The findings from the successful Rescheduling Application ("Successful Application") for Psilocybin for treatment-resistant depression dated 2 March 2022.

ii) Submission Opposing the Interim Decisions not to amend the Poisons Standard in Relation to the Restricted Medical Use of MDMA and Psilocybine dated 24 November 2022
iii) The Delegate's final decision to amend the current Poisons Standard in relation to Psilocybine and MDMA dated 3 February 2023

Proposed Controls

In line with the TGA's existing framework for Schedule 8 substances, we propose:

i) Prescription privileges limited to qualified practitioners (palliative care specialists, oncologists, or psychiatrists with relevant training).
ii) Administration solely in medically supervised settings, such as palliative care wards or approved clinical environments, with comprehensive patient monitoring.
iii) Mandatory training for clinicians and facilitators, including preparation and integration sessions to ensure safe and responsible use.

Such measures will preserve patient safety, minimise the risk of misuse, and uphold best-practice standards consistent with other tightly regulated therapies.

Patients approaching the end of life often confront profound existential distress that standard pharmacological or psychosocial interventions struggle to alleviate. Given the compelling trial data, Swiss clinical experience and well-established safety controls, we believe psilocybin-assisted therapy should be available to those who urgently need it.

Allowing psilocybin for this indication would reflect the same compassion and respect for patient autonomy that underpins the rationale behind VAD. We respectfully request that the TGA expand psilocybin's scheduling to include end-of-life existential distress, thereby granting patients a scientifically grounded, ethically managed option for relief at a time they need it most.

We are available to meet with the Therapeutic Goods Administration, the Advisory Committee on Medicines Scheduling and the nominated Delegate of the Secretary of the Department of Health at your convenience to discuss all aspects of our Application.

Thank you for considering this submission. We would welcome any opportunity to provide further information or collaborate on the development of guidelines ensuring safe and equitable access to psilocybin therapy for Australians in palliative care.

Yours sincerely,

Justine Topfer
Founder of the Palliative Care Psychedelic-Assisted Therapy Coalition
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Shanae O'Leary
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1. Applicant's details

Palliative Care Psychedelic-Assisted Therapy Coalition

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Justine Topfer: 0432 905 349

Shanae O'Leary: 0420 269 134

Name of the organisation you are representing for this application:
Palliative Psychedelic-Assisted Therapy Coalition with the support of Mind Medicine Australia.

2. Contact person's details

What is the name of the contact person:

Justine Topfer

Shanae O'Leary

What is the email address of the contact person:

justine@goodbyeandhello.com.au

shanaepsychology@gmail.com

What is the email of the contact person:

0432 905 349 (Justine Topfer)

0420 269 134 (Shanae O'Leary)

3. Substance details

3.1. What is the name of the substance?

Psilocybine

3.2. What are the alternative names of the substance?

Psilocybin

3.3. Is the substance a derivative of any currently scheduled poisons?

Psilocybin is not considered a derivative of any currently scheduled poison under the Australian Poisons Standard, because it is explicitly listed by name as “Psilocybin” (Schedule 9) rather than being subsumed under another compound’s derivative clause. Notably, the Therapeutic Goods Administration (TGA) clarifies in its *Poisons Standard* (the SUSMP) that psilocybin stands as a separate controlled substance, thereby confirming its status as an independently regulated chemical rather than a derivative (Therapeutic Goods Administration, 2023a). In addition, the TGA’s *Final Decisions and Reasons for Decisions* related to psilocybin confirm that it is scheduled on its own merits and not under the derivative provisions of any other scheduled poison (Therapeutic Goods Administration, 2023b). These regulatory listings highlight psilocybin’s distinct chemical identity ($C_{12}H_{17}N_2O_4P$) and underscore that it is not captured as a derivative of another scheduled substance.

3.4. What are the CAS numbers of the substance?

CAS Number: 620-52-5

3.5. Upload an image of the chemical structure of the substance

The chemical structure of Psilocybin is set out in Figure 1 below.

Figure 1 Chemical Structure of Psilocybin

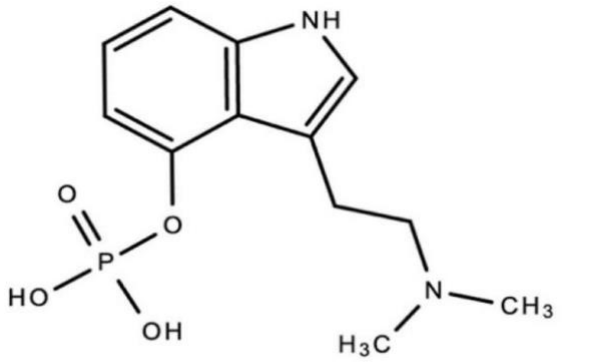

Illustration of molecular structure of Psilocybin (Lowe et al 2021)

The Chemical properties of psilocybin are set out in below.

Table 1. Chemical properties of Psilocybin:

Property	**Value**
Chemical Formula	$C_{12}H_{17}N_2O_4P$
CAS Number	620-52-5
IUPAC Name	[3-(2-dimethylaminoethyl)-1H-indol-4-yl] dihydrogen phosphate
Molar Mass	248.25 g/mol
Boiling Point	220-228°C

3.6. What are the known uses of the substance?

Psilocybin is primarily used as an adjunct to psychotherapy to enhance emotional and psychological processing under carefully controlled clinical conditions (Griffiths et al., 2016; Ross et al., 2016). Historically, psilocybin has also been employed by Indigenous communities for ceremonial, spiritual, and healing practices (Wasson, 1957; Schultes, 1969). These traditions aim to connect participants with ancestral knowledge, foster community cohesion and facilitate spiritual insight. While psilocybin is administered differently in clinical settings compared to Indigenous practices, its role in facilitating profound psychological and spiritual experiences remains central to both traditional and modern therapeutic applications. It is therefore essential to acknowledge that these traditions have influenced contemporary therapeutic models, reinforcing psilocybin's role in supporting transformative psychological experiences.

Known uses of Psilocybin in Modern Clinical Settings:

- Enhancement of emotions: Facilitates deeper affective awareness and empathy, potentially improving the therapeutic alliance and emotional insights (Griffiths et al., 2016).
- Increased introspection: Promotes self-reflection, making underlying cognitive or emotional patterns more accessible during therapy (Carhart-Harris et al., 2012).
- Expanded awareness of subconscious processes: Through guided psychotherapeutic support, individuals may gain access to repressed material or hidden emotional states (Ross et al., 2016).
- Induction of hypnagogic or dream-like experiences: Encourages non-ordinary states of consciousness, which can enhance creativity and personal insight (Carhart-Harris et al., 2012).
- Synaesthesia: Some users may experience cross-sensory perceptions (e.g., "seeing sounds"), contributing to deeper engagement in therapy (Passie et al., 2002).
- Labile brain state: Facilitates neural plasticity and openness to new perspectives, beneficial for addressing mood and anxiety disorders (Carhart-Harris et al., 2014).
- Alterations of thought and sense of time: May disrupt habitual cognitive loops, allowing patients to break free from maladaptive patterns (Ross et al., 2016).

- Encouragement of 'emotional breakthroughs': Enables the release of long-suppressed feelings and fosters profound catharsis in therapeutic contexts (Griffiths et al., 2016).

3.7. What are the proposed uses of the substance?

We request a limited therapeutic expansion for psilocybin to be used in treating existential distress towards the end of life. The Palliative Care Psychedelic-Assisted Therapy (PAT) Coalition and Mind Medicine Australia propose that psilocybin's Schedule 8 allowance (currently for treatment-resistant depression) be expanded to include this new indication. This would enable access via the Authorised Prescriber (AP) scheme for patients facing a terminal illness accompanied by severe existential or psychosocial suffering

Rationale & Framework

- *Robust Clinical Evidence:* Multiple international trials (NYU, Johns Hopkins, UCLA) have reported high safety and efficacy for psilocybin in addressing existential distress among patients with life-limiting illnesses. Additionally, Swiss compassionate-use experience since 2014 confirms that psychiatrists, oncologists, and palliative care specialists can safely incorporate psilocybin therapy under controlled frameworks to relieve end-of-life suffering (Aicher et al., 2024; Aicher & Gasser, 2024). These data support psilocybin as a viable therapeutic option where conventional treatments have limited effect.
- *Palliative Care & Patient Choice:* Modern palliative care emphasises patient autonomy in end-of-life decisions. Australia has acknowledged this autonomy through legal Voluntary Assisted Dying (VAD) in all six states. We argue that psilocybin-assisted therapy represents a similarly vital option for those experiencing unbearable existential distress. Given the strong clinical evidence for relief of spiritual and emotional suffering, it would be inconsistent and unethical to withhold this evidence-based therapy from mentally competent, terminally ill individuals who seek it. Patients capable of informed consent should have the choice of this therapy, just as they have choices about palliative treatments or even VAD.
- *Proposed Patient Population:* In line with inclusion criteria of existing clinical trials, we propose that eligible patients be adults (18+) diagnosed with a life-limiting illness (for example, advanced cancer) with an estimated prognosis of up to roughly 1,000 days (approximately 3 years). Ideally, patients should have at least 3–6 months remaining life expectancy to allow sufficient time for preparation, the psilocybin session, and integration therapy (ensuring continuity of care and maximising benefit) (Lewis et al., 2023). This window targets those in the advanced illness trajectory who are experiencing significant distress, while still early enough to engage in therapy meaningfully.
- *Prescribing & Training:* We propose that palliative care specialists (physicians with specialist qualifications in palliative medicine) will serve as the primary prescribers for this indication, reflecting their expertise in end-of-life care. These specialists would be required to undergo specific training in Psychedelic-Assisted Therapy (PAT) to become Authorised Prescribers for psilocybin. Oncologists and general practitioners with palliative care credentials could also apply for authorisation under the AP pathway. Psychiatrists, who currently lead psilocybin therapy for mental illness, would remain involved for patients with co-morbid serious psychiatric

histories, in such cases, a psychiatric assessment would be mandatory to screen for contraindications or unmanaged mental illness. This approach ensures that terminally ill patients without pre-existing psychiatric conditions can access psilocybin therapy without unnecessary hurdles, while those with complex mental health histories receive appropriate psychiatric oversight.

- *Informed Consent & Proposed Controls:* Under this framework, rigorous informed consent is paramount. Psilocybin-assisted therapy would be an optional intervention offered only to those who meet strict clinical and prognostic criteria and who fully understand the potential risks and benefits. No patient would ever be coerced to undergo this therapy. Additional safeguards include: administration only in medically supervised environments (e.g. hospital or clinic) with appropriate resuscitation facilities; close monitoring by trained therapists during preparation, dosing, and integration sessions; and restricted prescribing privileges, only practitioners approved under the TGA's Authorised Prescriber scheme and with specific PAT training can prescribe or administer psilocybin. These controls mirror those in place for the recently-approved use of psilocybin in treatment-resistant depression and ensure patient safety and public trust.

In preparing this application, the Palliative Psychedelic-Assisted Therapy Coalition and Mind Medicine Australia have taken into account:

- The findings from the successful Rescheduling Application ("Successful Application") for Psilocybin for treatment-resistant depression dated 2 March 2022.
- Submission Opposing the Interim Decisions not to amend the Poisons Standard in Relation to the Restricted Medical Use of MDMA and Psilocybine dated 24 November 2022
- The Delegate's final decision to amend the current Poisons Standard in relation to Psilocybine and MDMA dated 3 February 2023

Furthermore, we have reviewed developments since the 2023 approval of psilocybin for treatment-resistant depression, including new evidence that reinforces the urgent need for psilocybin-assisted therapy in palliative care settings, where existential distress is frequently intense and unmet by existing treatments.

3.8. What are the pack sizes of products marketed or supplied in Australia that contain the substance?

Currently, no TGA-registered psilocybin products are commercially marketed or supplied in Australia. Psilocybin is a Schedule 9 prohibited substance (outside of clinical trials or special access), so there are no established pack sizes on the Australian Register of Therapeutic Goods (ARTG). The latest Poisons Standard listings and a search of the ARTG show no entries for psilocybin-containing medicines, and thus no standard pack size exists in the Australian market at this time (Therapeutic Goods Administration, 2023a; Therapeutic Goods Administration, 2023b).

3.9. What are the proposed pack sizes for products that contain the substance?

At present, no formally approved pack sizes for psilocybin-containing products exist in Australia. Because no formal pack sizes exist yet, we look to clinical use patterns for guidance. Clinical trials and treatment protocols typically use single-dose 25 mg capsules of

psilocybin for adult patients (this dosage has become a de facto standard in research) (Carhart-Harris et al., 2021). We therefore propose a small pack size optimized for single administrations: for example, a blister pack containing one or two 25 mg capsules. This would correspond to one therapeutic session's supply (usually a single 25 mg dose, with a second capsule available if a lower dose or two-step dosing is needed). Each pack would be intended for a single patient use under direct medical supervision. This limited pack size minimises the amount of psilocybin in circulation and aligns with the controlled nature of therapy sessions. It also reflects current practice where each therapy session is individually prepared. The pack would only be supplied on the prescription or order of an authorised prescriber, such as a TGA-approved psychiatrist or palliative care specialist, who is permitted to administer psilocybin under current regulatory provisions.

3.10. In what forms do products containing the substance currently appear in Australia?

There are no approved commercial forms of psilocybin in Australia at present (no products listed on the ARTG). However, in clinical trials and authorised prescriber treatments, psilocybin is typically provided as oral capsules (usually 25 mg per capsule) for ease of dosing (Carhart-Harris et al., 2021; Therapeutic Goods Administration, 2023). These capsules contain synthetic psilocybin in a measured dose. Other dosage forms (e.g. tablets, liquid solutions, injectables) are not currently used or approved. Thus, the only form in use under experimental or special access conditions is a capsule for oral administration.

3.11. What are the proposed forms for products containing the substance?

We propose to source Good Manufacturing Practice (GMP) grade psilocybin that meets TGA Quality Guidelines (6 Jan 2025). Mind Medicine Australia (MMA) has facilitated arrangements for GMP-quality psilocybin to be available through an Australian pharmacy. The planned supply chain is as follows:

- **Sponsor/Importer:** MEPH Pharmacy Pty Ltd (157 Scoresby Rd, Boronia VIC 3155) – this pharmacy will handle importation and supply under proper licenses.
- **Manufacturer:** Optimi Health Inc. (21 Water St #600, Vancouver, BC V6B 1A1, Canada) – a manufacturer capable of producing pharmaceutical-grade psilocybin.

A certificate of analysis can be provided to authorised prescribers, such as a TGA-approved psychiatrist or palliative care specialist on request.

4. Purpose of application

4.1. What title would you like to give this application?

Application to expand the application of Psilocybin in the Poisons Standard to include existential distress towards end of life.

4.2. What type of change to the Poisons Standard are you requesting in this application?

Amend or add entries for a substance already included in the Poisons Standard

4.3. Provide an overview of your application in plain English

Psilocybin is a psychedelic substance historically classified as a Schedule 9 (prohibited) drug. In February 2023, the TGA made a landmark decision to down-schedule psilocybin to Schedule 8 (controlled medicine) for use in treatment-resistant depression (TRD) under

strict specialist supervision. This application proposes to expand that Schedule 8 permission to allow psilocybin-assisted therapy for existential distress in palliative care (i.e. distress in patients with terminal illnesses).

Multiple clinical trials have shown that psilocybin-assisted therapy can dramatically reduce anxiety, depression, demoralisation and fear of death in terminally ill patients (Ross et al., 2016; Griffiths et al., 2016. These benefits often endure for months up to years after just a single dose (Agin-Liebes et al., 2020; Ross et al., 2022). Treatment would be delivered under the same strict medical supervision as the current TRD use – via the Authorised Prescriber scheme, with specially trained doctors and controlled clinical settings – thereby ensuring safety and minimising any risk of misuse.

Allowing this use of psilocybin is in line with international precedents. For example, Canada's Special Access Program has begun permitting psilocybin for end-of-life distress on a case-by-case basis and leading U.S. cancer centers have conducted trials with compelling results. There is also strong ethical and compassionate rationale: patients at end of life often face extreme existential suffering that conventional medications and psychotherapy frequently fail to relieve. In Australia, while Voluntary Assisted Dying (VAD) laws provide an option to end life to escape suffering, psilocybin-assisted therapy offers an alternative: it can help patients find meaning, peace, and renewed engagement in life, even as life draws to a close. Many patients report that after psilocybin therapy they are more accepting of death and less frightened, which can improve their remaining time with family and reduce requests for hastened death.

In summary, this application seeks to enhance palliative care by making psilocybin-assisted therapy available to eligible terminally ill patients under stringent controls. By expanding the Schedule 8 entry for psilocybin to include "existential distress in patients with a terminal illness" we can compassionately address a critical unmet need. The change would maintain all existing safeguards (Authorised Prescriber approval, specialist oversight, etc.) that the TGA already requires for psilocybin's use in TRD. This is a measured, evidence-based and compassionate proposal to improve the quality of life of dying patients and ease profound psychological suffering where other interventions have proven inadequate.

5. Amendments to the Schedules of the Poisons Standard

5.1. In what Schedules of the current Poisons Standard is the substance included?

Schedule 8, Schedule 9

5.2. What is the current text for the substance as it appears in the Schedules of the Poisons Standard?

The Therapeutic Goods (Poisons Standard – 23 January 2025) lists psilocybin as follows:

Schedule 8 – Controlled drugs
PSILOCYBINE in preparations for human therapeutic use for the treatment of treatment-resistant depression.

Schedule 9—Prohibited substances
PSILOCYBINE **except** when included in Schedule 8.

5.3. In what Schedules of the Poisons Standard do you propose the substance to be included?

Schedule 8, Schedule 9

5.4. What text are you proposing for the substance in the Schedules and Index of the Poisons Standard?

Proposed Schedule Entries:

Schedule 9—Prohibited substances (no change to wording):
PSILOCYBINE **except** when included in Schedule 8.

Schedule 8 – Controlled drugs (amended/new entry for psilocybin):
 # PSILOCYBINE – *in preparations for human therapeutic use for the treatment of existential distress towards the end of life,* **when:**

a) used as part of psychotherapy in medically controlled environments; and

b) under the authorisation of a treating palliative care specialist who has received specific training; and

c) where the patient's diagnosis and proposed treatment plan is confirmed by at least one independent reviewing specialist doctor; and

d) where the substance has been manufactured in accordance with the Narcotic Drugs Act 1967; and/or

e) imported as therapeutic goods, or for use in therapeutic goods, for supply, in accordance with the Therapeutic Goods Act 1989; and/or

f) in therapeutic goods supplied in accordance with the Therapeutic Goods Act 1989.

Proposed Index Entry:
PSILOCYBINE
cross reference: PSILOCYBIN, CAS No. 520-52-5
Schedule 9
Schedule 8

6. Amendments to the Appendices of the Poisons Standard

6.1. In which Appendices of the current Poisons Standard is the substance included?

Appendix D, Appendix F

6.2. What is the current text for the substance as it appears in the Appendices of the Poisons Standard?

Appendix D—Additional controls on possession or supply of poisons included in Schedule 4 or 8

Item 5 Poisons for which possession without authority is illegal

The following table specifies poisons that must not be possessed by a person without authority (for example, possession other than in accordance with a legal prescription).

Item 31 PSILOCYBINE

Item 9 Poisons available only when prescribed or authorised in certain circumstances

PSILOCYBINE in preparations for human use may be supplied only for the treatment of treatment-resistant depression:

(a) if psilocybine is prescribed, or its supply is authorised, by a medical practitioner:

(i) registered under State or Territory legislation that forms part of the Health Practitioner Regulation National Law as a specialist psychiatrist; and

(ii) for whom an authority under subsection 19(5) of the Act that covers psilocybine is in force; or

(b) for use in a clinical trial that is approved by, or notified to, the Secretary under the Act.

Appendix F—Warning statements and general safety directions for poisons

1 Warning statements

Item 36 For use under medical supervision only

6.3. In which Appendices of the Poisons Standard do you propose the substance to be included?

Appendix D, Appendix F

6.4. What text are you proposing for the substance in the Appendices and Index of the Poisons Standard?

We propose to include (or retain) psilocybin in the same Appendices (D and F), with modifications to Appendix D entries to accommodate the new indication and prescriber group. Specifically:

Appendix D—Additional controls on possession or supply of poisons included in Schedule 4 or 8

3 Poisons available only from or on the prescription or order of a medical practitioner approved or authorised under section 19 of the Act

We propose adding Psilocybine to Item 3 (Item 3 ensures that only medical practitioners with a TGA Section 19(5) authorisation, i.e., Authorised Prescribers can prescribe or supply the substance. Including psilocybin here explicitly will reinforce that only authorised doctors may prescribe it, which now would include authorised palliative care specialists, not just psychiatrists)

5 (Poisons for which possession without authority is illegal): Psilocybine is already listed and should remain listed here

9 Poisons available only when prescribed or authorised in certain circumstances

We propose updating the psilocybin entry under Item 9 to add the new indication of treatment for existential distress toward end of life alongside treatment resistant depression and to broaden the prescriber criterion to include certain palliative care specialists (not only psychiatrists)

Appendix F—Warning statements and general safety directions for poisons
Psilocybin should continue to be included under Item 1 (Warning statements) with Statement 36: "For use under medical supervision only" (No change is needed here aside from ensuring this requirement remains in force for any psilocybin product used for the new indication. This warning is appropriate given the need for strict supervision)

Proposed Index:
PSILOCYBINE
Appendix D, clause 3 (Poisons available only from or on the prescription or order of a medical practitioner approved or authorised under section 19 of the Act)
Appendix D, clause 5 (Poisons for which possession without authority is illegal)
Appendix D, clause 9 (Poisons available only when prescribed or authorised in certain circumstances)
Appendix F, Part 1, Item 36

7. Details claims against the requirements of the scheduling criteria

7.1. What are the risks and benefits associated with the use of the substance?

Benefits of Psilocybin for Existential Distress: Contemporary Scientific Research

1) *Decreased Depression and Anxiety*

The Johns Hopkins Phase 2 Trial Investigating Psilocybin-Assisted Therapy For Anxiety and Depression Exacerbated by a Recent Cancer Diagnosis (Griffiths et al., 2016).
The trial results published in the Journal of Psychopharmacology in 2016 showed Psilocybin was an effective treatment for reducing depression and anxiety among patients with life-threatening cancer (Griffiths et al., 2016). The study involved 51 participants diagnosed with life-threatening cancer and experiencing clinically significant anxiety and/or depression.

Conducted as a randomised double-blind trial, participants received both a high dose (22 or 30 mg/70 kg) and a low placebo-like dose (1 or 3 mg/70 kg) of psilocybin in two separate sessions five weeks apart. Alongside the dose of psilocybin, participants received several preparatory and integrative psychotherapy sessions to prepare participants and help them process their psilocybin experience.

Findings from the included:
Depression:

- Statistically significant reductions in depression 5 weeks after a single high dose of psilocybin (GRID-HAMD-17: P<0.001; BDI: P<0.01; HADS-Depression: P<0.05).
- 92% of participants showed a clinical response; 60% achieved symptom remission in depression (measured by GRID-HAMD-17).
- Sustained effects at 6-month follow-up: 59–71% remained in symptom remission.

Anxiety:

- Statistically significant reductions in anxiety (HAM-A: P<0.001; STAI-Trait Anxiety: P<0.05).
- 76% of participants showed a clinical response; 52% achieved symptom remission in anxiety (measured by HAM-A).
- Sustained effects at 6-month follow-up: 50–63% remained in symptom remission.

The Harbor-UCLA Study Exploring Psilocybin-Assisted Therapy for Anxiety in Patients with Advanced-Stage Cancer (Grob et al., 2011)
The pilot study published in Archives of General Psychiatry in 2011 demonstrated that psilocybin significantly reduced anxiety and improved mood in patients with advanced-stage cancer (Grob et al., 2011).

This randomised, double-blind, placebo-controlled trial recruited 12 adults diagnosed with advanced-stage and aimed to evaluate the safety and efficacy of psilocybin in reducing anxiety among cancer patients. The trial was conducted in a controlled clinical setting at the Harbor-UCLA Medical Centre in California. Participants received preparatory psychotherapy sessions before the psilocybin-administered session. Participants acted as their own controls and received either a moderate dose of psilocybin (0.2 mg/kg) at one session and a placebo (250 mg of niacin) on the next. Participants then received monthly integrative psychotherapy for the 6-month follow-up period.

Findings included:
Trait Anxiety:

- Significant reductions at 1-month (t_{11} = 4.36, P = .001) and 3-month (t_{10} = 2.55, P = .03) follow-ups compared to placebo.

See attached document ‘Figures and Tables’ in Supporting Documents for a visual representation of changes in State (A) and Trait (B) anxiety (Figure 1)

Depression:

- Approximately 30% reduction in BDI scores from baseline to 1 month (t_{11} = –2.17, P = .05).

- Sustained reductions at 6-month follow-up ($t_7 = 2.71$, P = .03).

The NYU Psilocybin Trial for Treating Existential Distress in Cancer Patients: A Randomised Controlled Study (Ross et al., 2016)

The study published in the Journal of Psychopharmacology in 2016 demonstrated that a single dose of psilocybin, administered with supportive psychotherapy, significantly reduced anxiety and depression in patients with life-threatening cancer (Ross et al., 2016).

The study involved a total of 29 participants diagnosed with life-threatening cancer and experiencing clinically significant anxiety and depression. The trial was designed as a double-blind, placebo-controlled, crossover study to assess the effects of psilocybin on cancer-related psychological distress. Participants were randomly assigned to receive either a single dose of psilocybin (0.3 mg/kg) or an active placebo (niacin) during the first session, followed by the alternative treatment in the second session after a seven-week interval. The trial consisted of several sessions including preparatory and integrative psychotherapy sessions to support participants before and after each dosing session.

Findings included:
Depression:

- Statistically significant reductions 1 day (P<.001) and 7 weeks (P<.001) post-treatment (measured by BDI).
- Over 80% of participants achieved remission at both time points.
- Sustained effects at 6-month follow-up.

Anxiety:

- Statistically significant reductions 1 day (P<.05) and 7 weeks (P<.001) post-treatment (measured by HADS-A).
- Over 80% achieved remission at 6-month follow-up.

Long-Term Follow-up of The NYU Psilocybin Trial for Treating Existential Distress in Cancer Patients (Agin-Liebes et al., 2020)

In a long-term follow-up study published in the Journal of Psychopharmacology in 2020 reported significant reductions in existential distress 4.5 years after a single dose of psilocybin was administered alongside supportive psychotherapy (Agin-Liebes et al., 2020). 15 participants from their parent study (Ross et al., 2016) completed follow-up assessments 3.2 and 4.5 years after being administered a single moderate dose of psilocybin.

See attached document ‘Figures and Tables’ in Supporting Documents for a table of changes in depression and anxiety up to 4.5 years post-treatment (Table 1)

Summary of key findings:
Significant Reductions at 6.5–8 Months Post-Treatment:

- Anxiety (HADS, STAI-State, and STAI-Trait): Markedly reduced compared to baseline.
- Depression (HADS and Beck Depression Inventory): Significantly reduced compared to baseline.
- HADS Total Score: Substantial decrease compared to baseline.

Sustained Improvements at 3.2 and 4.5 Years:

- Anxiety and depression scores slightly increased at 3.2 years but remained significantly lower than baseline.
- Sustained reductions in anxiety (HADS Anxiety, STAI-State, and STAI-Trait) at 4.5 years.
- Depression (HADS and Beck Depression Inventory) scores remained significantly lower than baseline at 4.5 years.

Long-Term Therapeutic Benefits:

- Anxiety and depression reductions observed at 6.5 months were maintained over 4.5 years.
- Participants continued to report improved mental health outcomes compared to baseline.

The Compass Pathways Phase 2 Trial Exploring Psilocybin-Assisted Group Therapy for Major Depressive Disorder in Cancer Patients (Agrawal et al., 2023)

A recent phase 2 trial published in Cancer in 2024 explored the effects of psilocybin-assisted therapy on depression in patients with cancer and major depressive disorder (Agrawal et al., 2023). Conducted over an 8-week period, the study included 30 participants aged 30 to 78, all diagnosed with either curable or non-curable cancer. Each participant received a single 25 mg dose of psilocybin within a controlled, community oncology setting. The trial featured comprehensive psychological support, encompassing pre-treatment preparation sessions, individualised and group therapeutic sessions during psilocybin administration, and multiple post-treatment integration sessions. Depression and anxiety were assessed using validated scales, including the Montgomery-Asberg Depression Rating Scale (MADRS) and the Hamilton Anxiety Rating Scale (HAM-A), at baseline and at follow-up visits conducted at weeks 1, 3, and 8 post-treatment.

Results from the study indicated a substantial reduction in depressive symptoms.
The key finding from the trial were:

- 50% of participants experienced full remission of depressive symptoms by week 1, and this remission was sustained for at least 8 weeks following the psilocybin treatment (see Figure below)
- Significant reductions in anxiety symptoms, with a 66% decrease in Hamilton Anxiety Rating Scale (HAM-A) scores from baseline to week 8.

See attached document ‘Figures and Tables’ in Supporting Documents for a visual representation of changes MADRS scores (depression) from baseline to week 8 (Figure 2)

The HOPE trial (A Pilot Study of Psilocybin-Enhanced Group Psychotherapy in Patients with Cancer) (Lewis et al., 2023)

A recent pilot study conducted at the University of Utah explored the potential of psilocybin-assisted group therapy to alleviate depression in patients with cancer (Lewis et al., 2023) . The study involved 12 participants diagnosed with depressive disorders related to their cancer diagnosis. Each participant received a single high dose of 25 mg psilocybin during a group session, accompanied by three preparatory sessions and three post-

psilocybin integration sessions. The sessions were held over a three-week period, with the aim of supporting participants in processing their experiences in a therapeutic group setting.

The trial demonstrated significant reductions in depressive symptoms. Key findings include:

- Average HAM-D score decreased from 21.50 (±1.63) at baseline to 10.79 (±1.99) at the 2-week follow-up, representing a significant reduction in depressive symptoms.
- 50% of participants achieved remission (HAM-D < 7) at the 2-week follow-up.
- 6-Month Follow-Up HAM-D Score: Average score was 14.83 (±1.99), indicating that improvements in depressive symptoms were maintained, though less pronounced compared to the 2-week follow-up.

Usona Institute Randomised Clinical Trial Evaluating Repeated Doses of Psilocybin in Participants with Treatment Resistant Depression (Rosenblat et al., 2024)

The Usona Institute Randomised Controlled Trial aimed to determine the feasibility of Psilocybin-assisted psychotherapy in a complex populations, including high levels of treatment resistance in major depressive and bipolar disorder and patients with baseline suicidality and significant comorbidity.

Key findings include:

- Greater reductions in depression severity as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) were observed in the immediate treatment arm compared to the waitlist period arm with a large hedge's g effect size of 1.07 ($p < 0.01$).
- Repeated doses were associated with further reductions in MADRS scores compared to baseline.

The Compass Pathways Phase 2b multi-site trial using psilocybin for treatment resistant depression (COMPASS Pathways, 2021)

The COMPASS Pathways Phase 2b trial was the largest in history for the use of psilocybin assisted therapy, in this case for treatment resistant depression.

The key findings of the trial were:

- Psilocybin-assisted therapy 25mg vs 1mg: a difference of -6.6 points in change from baseline in MADRS total scores at week 3 ($p<0.001$), with a statistically significant difference seen from day 2 up to week 6
- Psilocybin-assisted therapy 10mg vs 1mg: a non-statistically significant numerical treatment difference of -2.5 points at week 3 ($p=0.184$)
- At least double the number of MADRS responders, remitters, and sustained responders with 25mg vs 1mg; rapid response and remission from day 2 to week 3
    - 36.7% (29 patients) in 25mg group showed response at week 3, compared with 17.7% (14 patients) in 1mg group
    - 29.1% (23 patients) in 25mg group were in remission at week 3, compared with 7.6% (6 patients) in 1mg group
    - 24.1% (19 patients) in 25mg group were sustained responders at week 12, compared with 10.1% (8 patients) in 1mg group

Several systematic reviews have reported reductions in depression and anxiety among patients nearing the end of life who received psilocybin combined with supportive psychotherapy

Vargas and collagues (2020):

- Psilocybin significantly more effective than placebo for anxiety and depression in end-of-life care.
- Considered safe and potentially a first-line treatment.

Bahi (2019):

- Psilocybin is safe and effective for cancer-related depression and anxiety after a single session.

Yu and colleagues (2021):

- Psilocybin more effective than placebo in reducing state anxiety at 1 day (g = –0.70) and 2 weeks (g = –1.03) post-treatment.
- Reductions in trait anxiety at 1 day (g = –0.71), 2 weeks (g = –1.08), and 6 months (g = –0.84).

2) *Decreased Demoralisation and Hopelessness*

The NYU Psilocybin Trial (Ross et al., 2016)

Secondary outcome measures of the NYU Psilocybin Trial focused on cancer-related existential distress, including demoralisation and hopelessness. Psilocybin, compared to the control, led to short-term reductions in demoralisation and hopelessness at 2 weeks post-dose 1, with these improvements remaining consistent at the 6-month follow-up, as assessed by the Demoralisation Scale and Hopelessness Assessment Inventory.

Long-Term Follow-up of the NYU Trial (Agin-Liebes et al., 2020)

Results from their long-term follow-up study show significant and lasting reductions in demoralisation and hopelessness following psilocybin assisted psychotherapy. Demoralisation scores dropped from 31.88 at baseline to 16.84 at 6.5–8 months and remained low at 3.2 years (13.29) and 4.5 years (14.32). Similarly, hopelessness scores decreased from 5.75 at baseline to 1.65 at 6.5–8 months, with sustained improvements at 3.2 years (2.29) and 4.5 years (1.65). These findings highlight the long-term effectiveness of psilocybin-assisted therapy in reducing cancer-related demoralisation and hopelessness.

See attached document ‘Figures and Tables’ in Supporting Documents for table of changes in cancer-related demoralisation and hopelessness (Table 2)

Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation (Ross et al., 2021)

A study published in Pharmacology & Translational Science in 2021 reported acute and sustained reductions in loss of meaning and suicidal ideation following psilocybin-assisted psychotherapy for psychiatric and existential distress amongst patients with life-threatening cancer (Ross et al., 2021). A sample of 11 participants from the parent trial (Ross et al., 2016) were included in the follow-up study. Significant reductions in hopelessness were

observed at the 6.5-month mark ($P < 0.001$). These improvements were sustained over time, with reductions in loss of meaning remaining significant at both 3.2 years and 4.5 years post-treatment ($P < 0.001$). These findings highlight the enduring impact of psilocybin-assisted therapy in addressing key aspects of existential distress.

The COMPASS Pathways Phase 2 Trial (Agrawal et al., 2023)
In their phase 2 trial Agrawal and colleagues observed substantial and sustained reduction in demoralisation following psilocybin-assisted therapy. The average DS-II score decreased by 45.5% at week 3 and further decreased by 46.9% at week 8. Both reductions were statistically significant ($P < 0.001$) and demonstrated large effect sizes, with Cohen's d values of 1.04 at week 3 and 1.02 at week 8. These findings demonstrated psilocybin's effectiveness in significantly reducing demoralisation.

See attached document 'Figures and Tables' in Supporting Documents for table demonstrating changes in cancer-related demoralisation (Table 3)

3) *Decreased Fear of Death*

The NYU Psilocybin Trial (Ross et al., 2016)
Secondary outcome measures of the NYU Psilocybin Trial focusing on anxiety and attitudes towards death had mixed findings regarding anxiety and attitudes toward death. At 2 weeks post-dose 1, psilocybin showed no significant impact on reducing death anxiety (DAS) or increasing death transcendence. However, by the 26-week final follow-up (post-dose 2), while death anxiety remained unchanged, significant improvements in attitudes and adaptations toward death (DTS) were observed in the psilocybin-first group compared to the niacin-first group.

Long-Term Follow-up of the NYU Trial (Agin-Liebes et al., 2020)
In their long-term follow-up study, participants demonstrated significant reductions in death anxiety at 6.5 months post-treatment, with these improvements remaining consistent at the 4.5-year follow-up.

See attached document 'Figures and Tables' in Supporting Documents for table demonstrating changes in death anxiety up to 4.5 years post treatment (Table 4)

4) *Decreased Suicidal Ideation*

Acute and Sustained Reductions in Loss of Meaning and Suicidal Ideation (Ross et al., 2021)
In their long-term follow-up study, significant reductions in suicidal ideation were observed at the 6.5-month mark ($P < 0.001$). A moderate positive correlation was found between loss of meaning and suicidal ideation ($r = 0.41$, $P = 0.02$), suggesting that as loss of meaning increased, so did suicidal ideation. Additionally, there was a strong correlation between reductions in suicidal ideation and decreases in depressive symptoms ($r = 0.75$, $P = 0.008$), highlighting the interconnectedness of these improvements.

5) *Decreased Physical Pain*

The COMPASS Pathways Phase 2 Trial (Agrawal et al., 2023)
The findings of this study demonstrate significant reductions in pain following psilocybin-assisted therapy. Pain VAS scores decreased decreased significantly from baseline to week 3 3 (P = 0.0050, Cohen's d = 0.45). Continued reductions were found at week 8 (P = 0.006, Cohen's d = 0.56). These results suggest that psilocybin-assisted therapy provides pain relief, with moderate effect sizes observed over the study period.

See attached document 'Figures and Tables' in Supporting Documents for table demonstrating changes decreased in physical pain (Table 5)

6) *Improved Existential Well-Being, including Death Acceptance, Quality of Life and Spiritual Wellbeing*

The Johns Hopkins Phase 2 Trial (Griffiths et al., 2016)
The Johns Hopkins Phase 2 Trial also included secondary outcome measures to understand whether single high dose of psilocybin, combined with preparatory and integrative psychotherapy, could impact measures existential distress.

Findings included:

- Statistically significant improvements in death acceptance (LAR-P = P<0.05)
- Statistically significant improvements in quality of life (MOQL = P<0.05)
- Clinically significant improvements in spiritual wellbeing (FACIT-Sp = P<0.001; Spiritual/Religious Outcome Scale = P<0.001)
- Observer ratings found clinically significant positive changes in attitudes and behaviour (P<0.001)
- Clinically significant improvements in spiritual well-being (FACIT-Sp: P < 0.001).
- 70% rated the experience among the top five most spiritually significant in their lives.

The NYU Psilocybin Trial (Ross et al., 2016)
The NYU Psilocybin Trial demonstrated significant reductions in existential distress, including notable improvements in spiritual well-being and quality of life. These findings were observed at 2 weeks post-treatment and sustained at the 6-month follow-up. These findings highlight the potential long-term benefits of psilocybin-assisted therapy in addressing existential challenges and enhancing overall well-being.

Long-Term Follow-up of the NYU Trial (Agin-Liebes et al., 2020)
The long-term follow-up (LTFU) assessments revealed significant improvements in spiritual well-being and faith domains (FACIT-Sp-12) compared to baseline. Quality of life outcomes were mixed: psychological and environmental dimensions improved at the first LTFU, but psychological gains were not sustained at the second LTFU. Participants reported enduring positive effects from the psilocybin experience, with 71% rating it as one of the top-five most personally meaningful experiences of their lives and 96% as one of the top-five most

spiritually significant. Additionally, 86% of participants attributed increased life satisfaction and well-being to the psilocybin session, demonstrating its lasting impact.

The COMPASS Pathways Phase 2 Trial (Agrawal et al., 2023)
In their phase 2 study, Agrawal and colleagues observed significant reductions in existential distress. Scores on the Sheehan Disability Scale (SDS) decreased by 58.9% from baseline to week 3 and then by an additional 8.0% from week 3 to week 8. Similarly, scores on the EQ-5D-5L decreased by 25.0% from baseline to week 3 and then by an additional 11.5% from week 3 to week 8. These findings highlight the effectiveness of PAP in reducing existential distress.

See attached document 'Figures and Tables' in Supporting Documents for table demonstrating changes in existential distress (Table 6)

The Compass Pathways Phase 2 Study Investigating Psilocybin-Assisted Therapy for Psycho-Social-Spiritual Well-Being in Cancer Patients with Major Depressive Disorder (Shnayder et al., 2023).
The Compass Pathways Phase 2 trial published in the Journal of Affective Disorder in involved 30 cancer patients diagnosed with major depressive disorder (Shnayder et al., 2023). The study aimed to evaluate the impact of psilocybin-assisted therapy on psycho-social-spiritual well-being. Participants received a single fixed dose of 25 mg psilocybin, along with comprehensive psychotherapy, including pre-treatment preparation, the psilocybin session, and post-treatment integration. Changes were assessed at baseline, day 1, week 1, week 3, and week 8 post-treatment.

Key findings indicated that all three factors of the NIH-HEALS (Connection, Reflection & Introspection, and Trust & Acceptance) showed significant improvements from baseline. The Connection factor increased by 12.7% (from 30.8 to 34.7; $p = 0.003$), Reflection & Introspection by 7.7% (from 55.7 to 60.0; $p < 0.001$), and Trust & Acceptance by 22.4% (from 32.6 to 39.9; $p < 0.001$). The cumulative NIH-HEALS score increased by 16.4 points from 119.1 at baseline to 134.6 at week 8 ($p < 0.001$). These results suggest that psilocybin-assisted therapy was associated with substantial and sustained improvements in psycho-social-spiritual well-being in this patient population.

The University of Utah Trial (Lewis et al., 2023)
In their study on psilocybin-assisted group therapy for depression in cancer patients, significant improvements were observed in existential well-being. This included enhancements in emotional ($P = 0.044$), functional ($P = 0.018$), and spiritual domains, such as spiritual meaning ($P = 0.030$), peace ($P = 0.016$), and faith ($P = 0.035$). While physical well-being also improved, it did not reach statistical significance ($P = 0.074$).

Risks/Adverse Effects

No drug-related serious adverse events (SAE) have been reported from any previous research investigating the effects of psilocybin in healthy participants (Aday et al., 2020).

In clinical trials there have been no reported SAE either pre- or post prohibition.

In its Final Decision the Delegate concluded that "... the safety profile of psilocybin under tightly supervised psychotherapy conditions used in clinical trials is quite reasonable" and acknowledged that "...the risk of addiction is low in a highly controlled environment for psilocybin assisted therapy."

All adverse effects in the studies were appropriately managed with safeguards in a clinical setting. The most common psychological adverse experiences have been anxiety and negative mood (Brown et al., 2017). The most common physical adverse events are cardiovascular (mild to moderate increases in blood pressure and heart rate), occasional nausea and headache.

There have been a number of recent clinical trials that confirm the strong safety profile of psilocybin when used as part of therapy in properly controlled environments including:

The Compass Pathways randomised Phase 1 double-blind placebo- controlled healthy persons trial

The Compass trial, conducted by King's College London (Carhart-Harris et al., 2021) and published in the *Journal of Psychopharmacology* on January 4, 2022, investigated psilocybin in a double-blind study with 89 healthy adult volunteers. Participants were randomised to receive 10 mg (n = 30), 25 mg (n = 30), or placebo (n = 29), with 1:1 support from a trained therapist during a six-hour session. A total of 25 dosing sessions, with up to six participants per session, were followed by a 12-week monitoring period. No serious adverse events occurred. Common side effects with 10 mg and 25 mg doses included sensory perception changes and positive mood orientation, with no negative impacts on cognition or emotional functioning.

See attached document 'Figures and Tables' in Supporting Documents for table detailing most frequently reported adverse effects (Table 7)

The Imperial College Phase 2 Trial comparing Psilocybin assisted psychotherapy with a leading SSRI plus therapy published in the New England Journal May 2021

A Phase 2 study completed in 2021, shows that psilocybin has similar primary efficacy at treating depression when compared to escitalopram (an SSRI antidepressant) and more favourable secondary effects, with twice as many patients going into remission from the psilocybin group and significantly less side effects.

This trial again showed Psilocybin to be well tolerated, this time amongst depression patients.

See attached document 'Figures and Tables' in Supporting Documents for table detailing adverse events reported during 6-week trial period and on dosing-day 1 (Table 8)

The Compass Pathways Phase 2b multi-site trial using psilocybin for treatment resistant depression released in November 2021

The COMPASS Pathways Phase 2b trial was the largest in history for the use of psilocybin assisted therapy, in this case for treatment resistant depression (COMPASS, 2021). The key findings of the trial were:

- Psilocybin-assisted therapy 25mg vs 1mg: a difference of -6.6 points in change from baseline in MADRS total scores at week 3 ($p<0.001$), with a statistically significant difference seen from day 2 up to week 6.
- Psilocybin-assisted therapy 10mg vs 1mg: a non-statistically significant numerical treatment difference of -2.5 points at week 3 ($p=0.184$)
- At least double the number of MADRS responders, remitters, and sustained responders with 25mg vs 1mg; rapid response and remission from day 2 to week 3:
    - 36.7% (29 patients) in 25mg group showed response at week 3, compared with 17.7% (14 patients) in 1mg group
    - 29.1% (23 patients) in 25mg group were in remission at week 3, compared with 7.6% (6 patients) in 1mg group
    - 24.1% (19 patients) in 25mg group were sustained responders at week 12, compared with 10.1% (8 patients) in 1mg group

Psilocybin was generally well tolerated, with >90% of adverse events mild or moderate, occurring primarily on or shortly after the dosing day (e.g., headache, nausea, fatigue). Hallucination-related events resolved the same day. Suicidal ideation, behaviour, and self-injury occurred across all groups, consistent with this population.

See attached document 'Figures and Tables' in Supporting Documents for table detailing most frequent adverse effects (Table 9)

The Compass Pathways Phase 2 Open Label Trial Investigating Psilocybin-Assisted Therapy for Psycho-Social-Spiritual Well-Being in Cancer Patients with Major Depressive Disorder: Adverse Effects and Safety

The Compass Pathways trial published in the Journal of Affective Disorder (Shnayder et al., 2023) showed that Psilocybin was well-tolerated. Mild to moderate adverse effects during the psilocybin-administered session.

Key findings include:

- The most common side effects included headaches (80%), nausea (40%), tearfulness (27%), anxiety (23%), euphoria (23%), fatigue (23%), and mild impairment of psychomotor functioning (10%). All these effects were temporary and resolved prior to discharge.
- No participants reported severe adverse effects, and there were no notable changes in laboratory results, electrocardiograms (ECGs), or suicidality.

Usona Institute Randomised Clinical Trial Evaluating Repeated Doses of Psilocybin in Participants with Treatment Resistant Depression: Safety and Efficacy (Rosenblat et al., 2024)

The Usona Institute Randomised Controlled Trial reported that adverse events from psilocybin were transient, with no serious adverse events, in patients with adults with treatment depression. See

See attached document 'Figures and Tables' in Supporting Documents for table detailing adverse effects (Table 10)

The Johns Hopkins Phase 2 Trial investigating psilocybin-assisted therapy for anxiety and depression exacerbated by a recent cancer diagnosis

The 2016 *Journal of Psychopharmacology* trial (Griffiths et al., 2016) found psilocybin to be well tolerated in cancer patients. Safety was ensured through careful screening, supervised sessions, and integration support. Adverse effects, including transient anxiety, vomiting, and fear or confusion, were mild to moderate. No long-term adverse effects were reported at the 6-month follow-up.

See attached document 'Figures and Tables' in Supporting Documents for table detailing adverse effects (Table 11)

NYU Randomised Controlled Trial Following Psilocybin Trial for Treating Existential Distress in Cancer Patient: Adverse Effects and Safety at Post-Treatment and Follow-up
The 2016 *Journal of Psychopharmacology* trial (Ross et al., 2016) demonstrated psilocybin's safety cancer patients. Cardiovascular measures (BP, HR) were monitored throughout, with key findings including:

Key findings include:

- No serious adverse events (AEs) attributed to psilocybin or niacin.
- No abuse, addiction, prolonged psychosis, or need for psychiatric hospitalisation.
- Common AEs: mild BP/HR elevations (76%), headaches (28%), nausea (14%), transient anxiety (17%), and psychotic-like symptoms (7%).
- No serious cardiac events or adverse effects reported at the 26-week follow-up.

13 participants completed long-term follow-ups as part of a parent study (Agin-Liebes et al., 2020). None of the participants reported lasting negative or adverse effects from the psilocybin-assisted therapy experiences.

The Harbor-UCLA Pilot Study Exploring Psilocybin-Assisted Therapy for Anxiety in Patients with Advanced-Stage Cancer
The 2011 *Archives of General Psychiatry* pilot trial found psilocybin to be well tolerated, with no sustained adverse effects or significant clinical concerns. Heart rates peaked at 81.5 bpm, and blood pressure (138.9/75.9 mm Hg) increased 2 hours post-administration but returned to baseline within 4–6 hours. These short-lived physiological changes were deemed safe, with no clinical interventions required.

The Compass Pathways Phase 2 Open-Label Trial Exploring Psilocybin-Assisted Group Therapy for Major Depressive Disorder in Cancer Patients: Adverse Effects and Safety
The Compass Pathways trial results published in *Cancer* in 2024 reported no serious adverse effects were attributed to psilocybin and treatment-related adverse effects were generally mild or expected (Agrawal et al., 2023).

See attached document 'Figures and Tables' in Supporting Documents for table detailing adverse events reported in Phase 2 Open-Label Trial investigating psilocybin assisted therapy for anxiety and depression exacerbated by recent cancer diagnosis (Table 12)

The University of Utah Pilot Study on Psilocybin-Assisted Group Therapy for Depression in Cancer Patients: Adverse Effects and Safety

The phase 2 study published in the Journal of Pain and Symptom Management showed no serious medical or psychiatric adverse events attributed to psilocybin (Lewis et al., 2023).

See attached document 'Figures and Tables' in Supporting Documents for table detailing adverse events reported in Phase 2 Trial investigating psilocybin assisted group psychotherapy for patients with cancer (Table 13)

7.2. What are the purposes for which the substance is to be used and the extent of use of the substance?

Purpose

Psilocybin is proposed for use in palliative care to address existential distress in patients with serious or life-limiting illnesses. This distress often manifests as profound anxiety, hopelessness, demoralisation and an overarching fear of death, symptoms that can significantly erode quality of life and exacerbate physical suffering in the terminal phase.

By leveraging psilocybin's demonstrated therapeutic effects within a structured, medically supervised framework, this intervention aims to:

- Alleviate psychological and spiritual suffering in terminally ill patients.
- Restore autonomy and meaning during the terminal phase of illness, aligning with the broader goals of compassionate end-of-life care.
- Foster emotional and existential wellbeing, enabling patients to engage more fully in end-of-life decision-making and interpersonal relationships.
- Complement existing palliative care measures by targeting the existential dimension of suffering, which conventional pharmacotherapies and supportive treatments often fail to address fully.

Extent of Use

- Prevalence of Need: Research indicates that up to one-third of individuals with advanced cancer or similarly severe conditions report significant existential distress (Bunn et al., 2023; Mitchell et al., 2011).
- Target Population: Adults (18+ years) diagnosed with life-limiting illnesses, ideally with a prognosis of up to 1,000 days and at least 3–6 months remaining, allowing sufficient preparation, dosing, and integration sessions.
- Potential Reach: While psilocybin is presently confined to clinical research and Authorised Prescriber or Special Access pathways, expanding its use to palliative care contexts could provide critical relief to a sizable subgroup of patients who find standard options inadequate for existential suffering.

In offering this purpose-driven approach, psilocybin-assisted therapy aligns with the core values of palliative care: to relieve suffering and optimise quality of life for those approaching the end of life.

7.3. What is the toxicity of the substance?

Psilocybin has demonstrated a very low toxicity profile under controlled conditions. Based on animal studies and extrapolations to humans, the lethal dose of psilocybin is estimated to be approximately 6 g, which is roughly 240 times the typical therapeutic dose of 25 mg

(Gable, 2004). In animal models, the median lethal dose (LD_{50}) ranges from 285 mg/kg in mice to 12.5 mg/kg in rabbits. Toxicity table included in section 'Toxiciyu Information'

Notably, no serious adverse events have been reported in clinical trials where psilocybin was administered under professional supervision (Grob et al., 2011; Griffiths et al., 2016; Ross et al., 2016). Although some participants experienced mild, transient effects such as elevated blood pressure, headache, or anxiety, these resolved without long-term complications.

7.4. What is the dosage, formulation, labelling, packaging and presentation of the substance?

Standard clinical practice uses single oral doses (often 25 mg). Typically labeled for supervised single-dose administration (Carhart-Harris et al., 2021).

7.5 What is the potential for the substance to be misused or abused?

Psilocybin has been assessed as having minimal potential for misuse or abuse when used in a controlled, clinical setting. According to the TGA's Final Decision (February 2023), there was no evidence from available clinical trial data to suggest that psilocybin leads to drug-seeking behavior, dependence or significant diversion when administered under strict medical protocols such as the Authorised Prescriber scheme. This conclusion is further supported by controlled studies (e.g., Griffiths et al., 2016; Ross et al., 2016) that report only transient, manageable side effects without any indication of compulsive use. Furthermore, the Independent Expert Panel's review on MDMA and psilocybin (Department of Health, 2021) reinforces that when these substances are administered within rigorously supervised therapeutic frameworks, the risk of misuse is negligible. Together, these findings indicate that, under comprehensive clinical supervision, psilocybin poses a very low risk of misuse or abuse.

7.6. Are there any other matters that may be necessary to protect public health?

We propose a tightly regulated therapeutic framework to ensure psilocybin-assisted therapy remains both safe and effective for end-of-life existential distress. Key safeguards include:

1) *Restricted Prescribing & Controlled Settings*

Prescription rights limited to palliative care specialists, oncologists, or GPs with palliative care training, all of whom must meet Authorised Prescriber requirements. The authorised prescriber will be supported in the provision of treatment by a dyad of PAT trained therapists.

Psilocybin administration confined to clinics or hospitals where oversight, patient support, and immediate clinical intervention are available if needed.

2) *Training Standards*

Practitioners must undergo targeted training in psilocybin-assisted therapy. As an oncologist in the UK notes (Bunn report, p. 46): *"People who are sitting or facilitating must be sufficiently well trained... having done enough work on themselves that when someone comes in contact with difficult material you don't turn away."*

Beyond didactic learning, self-awareness and emotional resilience are essential for facilitating safe, empathetic care (Bunn report, 2023). Some experts also suggest personal experience with psilocybin, under licensed supervision, can enhance a practitioner's ability

to guide patients through altered states of consciousness (Green et al., 2014; Larrison et al., 2011).

3) Ethical & Clinical Safeguards

Patient autonomy and informed consent: Ensuring individuals fully understand the therapy, associated risks, and possible outcomes, and can opt in or out freely.

Mental capacity assessments for patients with potential cognitive decline or compromised decision-making abilities, following standard Australian guidelines.

Comprehensive screening for severe mental illness, with psychiatric consultation required only when indicated, consistent with palliative care best practices.

Collectively, these measures maintain public health protections and uphold regulatory best practices for a psychoactive substance, ensuring psilocybin-assisted therapy is administered responsibly and with the necessary level of clinical and ethical rigor. As noted in the Delegate's 2023 Final Decision, the introduction of prescribing rights and stringent treatment protocols for psilocybin under a Schedule 8 classification effectively mitigates the risks previously highlighted in the interim decisions. Concluding this point, the Delegate stated that "the benefits to patients and public health of my final decisions will therefore outweigh the risks."

We strongly urge the Delegate to recognise the benefits of psilocybin-assisted therapy for terminally ill patients experiencing profound existential distress, as well as for their families. By expanding the Poisons Standard to include existential distress as an application for psilocybin use, we can ensure these vulnerable individuals receive compassionate, evidence-based support under a rigorous regulatory framework during the most challenging phase of life.

7.7. Would you like to provide any other information to support your application to amend the Poisons Standard?

1) Choose Your Own Ending

A GP who works in a palliative care ward, Dr Janelle Trees (J. Trees and J. Topfer, personal communication, 2024) shared the following de-identified account of a patient's experience of existential distress towards the end of life; then a conversation with the same patient who experienced psychedelic assisted therapy as a participant in a trial. Her patient has given permission to share their story.

"I'm stuck here in this sterile room. It's too cold. Turn the aircon off, will you? I do feel like a prisoner of this hospital. There's a heavy weight pressing down on me. Like I'm suffocating. It's hard to breath. But it's not just physical…
The incessant machines beep. The nurses rush around. All of it's like a constant reminder of my fragile, failing existence.
Stage IV cancer has metastasised to my bones. The pain is constant. Medicines take the edge off but it's always there waiting to grab me. Fatigue is the worst and there's nothing for that.

My body aches like the first few days of the flu. Never goes away. The physicality is hard to bear. It's compounded by what's going on in my head. I feel like cutting my head off sometimes. I'd like to put it in a jar with a lid!
I get midazolam to break the loop. Sometimes doze on it for an hour or two. I'm sedating myself. I know it's not good to want to sleep through the rest of my life. But what does life have to offer now?
It's my 50th birthday next week, and I can't be sure that I want to see it. The docs have been frank. One told me I won't make it to my daughter's 10th birthday next month. I believe them. I don't even cry about it anymore.
Yeah, I have questions with no answers. What was the purpose of my life? Did my life make any difference? Will anything I've done matter once I'm gone? All that energy I spent on things that didn't matter. What was the point of all that?
My impending death looms. I appreciate being able to talk to you about that. I suppose you hear it all the time, huh?
It's This feeling of doom. It casts a shadow on every memory, every achievement, really. It's shit. I've been depressed before. Grieved. This is harder. I'm standing on the edge of an abyss, staring into the unknown, and the abyss is staring back at me! I have no idea what's ahead I think it's nothing, truth be told. Oblivion.
Yeah, it gnaws away at my sanity! It's a relentless beast. I'm just flat. It's all emptiness inside. I don't know if I have a soul anywhere.

Look, it's true what you say. In all the despair, there's a flicker of hope. A tiny possibility of something else. I cling to that. Sometimes that illusion keeps me alive, I'm sure. I'm like a refugee hanging onto a piece of wood. Then it's gone. I'm smashed. I'm drowning.

In the end there's nothing. Daunting thoughts, fears, and the overwhelming certainty of dying soon. It's horrible and it's boring. It's taking too long. In the grand scheme of things, my existence is but a fleeting moment in the vast expanse of time. Nothing matters. You know that, don't you?"

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"I'm facing my mortality. That spark I told you about? It's brighter since I've embarked on this different sort of journey—into the mystical realms of psychedelics.
I'd like to be able to tell what it's like. It's a nice place. There's soft light and plenty of pillows. I hear birds and the wind outside. Kind people have music for me.'
I open myself to the profound wisdom these substances offer. With each intake, I'm transported beyond the confines of my physical form, transcending the limitations of time and space. It's scary but I love it. I'm free!
My existential distress dissolves into the ether; it's replaced by a profound sense of interconnectedness with the universe. No longer am I a mere speck in the cosmic expanse, I'm a vibrant thread woven into the fabric of existence.
Visions dance before my eyes. It's all a tapestry of profound insight and understanding. I can't describe it. I can say that the boundaries between myself and others, my environment, this world blur. And I am filled with empathy and compassion for all living beings. Like trees. Even rocks and soil.

I understand now what people mean by a sacred space. I confront the questions that haunted me. I'm working my way through to clarity and grace. It feels new but old at the same time. Coming out of this, I've remembered a reality that's true and real and infinite.
I embrace the impermanence of life. That's the essence of its beauty! None of this makes any sense if we don't move back to where we came from. There's meaning and love beyond this life, you know. I can't explain it if you haven't experienced it. I can't give that to you, but it's real.
I am filled with an overwhelming sense of gratitude for the opportunity to experience the wonders of existence. And to share that wonder with my daughter and other people.
From deep inside I have a profound sense of peace and acceptance. Fear gives way to awe.

I'm emerging from this transformative experience with a renewed sense of purpose and vitality.

My metastatic bone pain is still unrelenting, but it's tolerable now. It's okay that I may not live to my 50th birthday. If I don't I know that my daughter and husband will celebrate it for me. I've written a card for my daughter's 10th birthday next month, and letters for her to open for the next ten. I know that I'll forever live in her and with her. Love and learning are the only constants in this infinite universe. And my experience, who I am and what I've learned, will go on.

The experience of psychedelic assisted therapy helped me remember that I've lived fully. I've known love – plenty of it. I've embraced the challenges of existence in all its complexity. I am at peace with the life that I've lived and what lies ahead".

2) *Definition of Existential Distress*

Human consciousness provides both the unique awareness of impending death alongside a cognitive buffer which serves to distance this knowledge from daily streams of consciousness. Acknowledging our mortality can be weighty; it forces us to confront the finite nature of our existence. We often shy away from introspection about mortality, our mortality, my mortality, because it challenges our continuous experience of existence; nonexistence is in many ways incomprehensible. It disrupts our sense of invincibility and our pursuit of immediate, more pressing desires. Instead, we prefer to dwell in the comfort of the present, postponing such contemplation for another day, However, in the back of our minds there is a quiet but nagging inevitability. When will that day be that we are confronted with our mortality?

Our lack of societal dialogue and general unpreparedness for death is ironic as this avoidance causes us to lose the power to choose what we actually want our death to be like. Let's begin to shift the emotional stronghold and the societal stigma that we hold about death and dying. We can create a cultural shift to transform our thinking about serious illness, caregiving, grief and the end of life.

Existential Distress (ED) is defined as psychological turmoil in the face of imminent death that can have a multi-dimensional impact on one's physical, personal, relational, and spiritual well-being (Pessin et al., 2015). Symptoms include depressed or anxious mood,

demoralisation (hopelessness, and helplessness), fear, dread, rumination, angst, sleeplessness, anger, confusion and hallucination (Bunn et al., 2023).

Demoralisation syndrome was first described in the 1950s by Jerome Frank as a total sense of powerlessness to change oneself or one's environment, akin to hopelessness (de Figueiredo, 2007). It's clinical manifestation can range in severity from a feeling of disheartenment to a stronger loss of meaning and purpose (Bovero et al., 2023).

Loss of meaning and self identity, lack of purpose, fear of being a burden to others, a diminished sense of dignity, desire for death or lack of will to live are also common. Fear of being a burden on others, or "unworthy dying" rates (much) higher than fear of pain. (Bunn, 2023)

Prevalence of ED is reported to be as high 51.8% in patients with cancers (Bovero et al., 2023) ED is common in palliative care patients (Woźniewicz et al., 2023).

The Death and Dying Distress Scale (DADDS) and the Patient Dignity Inventory (PDI) are reliable tools for measuring existential distress and have been used to capture data regarding the experience of those approaching death (Bunn, 2023).

Existential distress is distinct from anxiety disorders because its explicit focus is on a life-threatening disease. It is a rational and human response to the great unknown of death. However, this shift of mental state is unconsciously preventing the terminally ill to make the most of what little time they have left. ED erodes quality of life.

Fear doesn't prevent death, it prevents a full life.

In this application we will outline the ethics, evidence and logic for extending TGA approval of psilocybin to include the indication of existential distress for those with a terminal illness. Additionally, to permit palliative care physicians and other specialist doctors and GPs working in palliative care who have had appropriate training to legally prescribe psilocybin for use within the context of psilocybin assisted therapy.

3) Prevalence of Existential Distress Toward End Of Life

Existential distress is more common than pain alone, towards the end of life. It is debilitating and prevalent in one-third of patients with cancer diagnoses (Mitchell et al., 2011). Ross et al., (2021) found existential distress can exacerbate existing nausea, pain or sleep difficulties.

A study by Rosenstein and colleagues (2011), examining the impact of depression on cancer patients found that those with depressive symptoms had a 26% higher mortality rate and those diagnosed with a major depressive disorder a 39% higher mortality rate.

A meta-analysis by Pinquart and Duberstein (2010) found that symptoms of depression and anxiety in palliative care populations are associated with increased mortality rates and with shorter survival times. For people suffering from depression towards the end of life there is

additional evidence of increased of rates of suicide (Pinquart and Duberstein, 2010). In addition, there is emerging evidence that poor mental health in people diagnosed with a terminal illness impacts their health and well-being, including the increased probability of development of a psychiatric disorder in their family, friends and particularly caregivers (Karabekiroğlu et al., 2018).

Caregivers have high rates of anxiety and depression. There is a decrease in their own survival associated with patient distress. Caregiver depression and anxiety are associated with the severity of the patient's physical and mental illness (Rhee et al., 2008).

4) Palliative Care Treatment Options & Efficacy

Palliative care is explicitly recognised as an aspect of the international human right to health (World Health Organisation, 2020). Person-centred and integrated health services paying special attention to the specific needs and preferences of individuals are intrinsic to palliative care. Physical, psychosocial and spiritual healthcare is an international human right.

The World Health Organisation (WHO) describes palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual." (WHO Palliative Care Fact Sheet, 2020).

The primary aim of palliative care is to enhance the quality of life for individuals facing serious illnesses, focusing on providing relief from the symptoms, particulalry (but not only) pain, and other stressors that accompany their condition. It aims to address not only physical discomfort but also the emotional, social, and spiritual needs of patients and their families.

The founder of the modern hospice movement, Dame Cicely Saunders, was among the first to characterise the diagnosis of 'total pain', which included the physical, emotional, social and spiritual dimensions of distress. Total pain carries with it existential distress and has been articulated as the disintegration of the self.

The amelioration of existential distress accompanying a terminal diagnosis is currently confined to psychological therapies, including creative therapies, and pharmacological interventions. However, the effectiveness of these treatments has been demonstrated to be modest in both controlled trials and in clinical palliative care settings (Faller et al., 2013; Zimmermann et al., 2008).

Pharmacotherapies

Pharmacological interventions are usually used, including antidepressants, antipsychotics and sedatives, when existential distress is unbearable (Trees, 2024).
Selective Serotonin Reuptake Inhibitors (SSRIs) are the most commonly used pharmacological treatment for depression and are often prescribed to people with a terminal diagnosis. However, a Cochrane review found research on the efficacy of these drugs in treating depression in cancer patients to be sparse. The clinical response to anti-

depressants (AD) is delayed, relapse is common, and meta-analyses of placebo-controlled trials of ADs for major depression in the context of cancer found no clear superiority of ADs over placebo (Ostuzzi et al., 2018).

Approximately 30% of individuals with depression, including those without a terminal diagnosis, do not respond to traditional antidepressants (Tweedy, 2022), and those who do may quickly develop dependence and adverse side effects. Relapse rates are also high. A randomised, double-blind trial published in the New England Journal of Medicine (Lewis et al., 2021) found that by 52 weeks, relapse occurred in39% in the maintenance group (those who continued taking SSRIs) vs 56% in the discontinuation group (those who had discontinued the SSRIs).

Additionally, Dr Janelle Trees reports that in clinical practice SSRIs, and other commonly used medications like antipsychotics (e.g quetiapine or olanzapine) and sedatives (e.g benzodiazepines or haloperidol) can lead to blunting of emotional states, which may impede the patient's ability to address the underlying trauma that is causing the symptoms of existential distress. Pharmacologically-induced obtundation of consciousness towards the end of life can distress and traumatise surviving loved ones.

Psychotherapy

Therapeutic supportive psychotherapy can provide individuals with a safe space to explore their existential concerns, find meaning, and come to terms with their mortality. But a Cochrane review focusing on incurable cancer patients concluded that "There is insufficient high-quality evidence supporting the effectiveness of psychotherapy for patients with clinically diagnosed depression" (Okuyama et al., 2017).

Mindfulness, Music and Related Therapies

Bunn and colleagues (2023) reviewed a range of non-clinical interventions to improve the mental health and quality of life of people with terminal diagnoses. Such interventions provide avenues for self-expression and emotional processing. They include various forms of group therapy, mindfulness, exercise, music and art therapies.

Although evidence suggests these interventions can yield small to moderate improvements in quality of life (Matis et al., 2020), they have primarily been tested in individuals without mental health conditions (with some trials even excluding individuals with such a diagnosis). As such, there are insufficient grounds to consider these as an intervention to support terminal patients also suffering from moderate-to-severe psychopathology or at heightened risk of suicide.

Creative therapies are often unavailable to palliative patients and their carers. When available, they are often charity-or volunteer-based, particularly (but not only) in regional, rural and remote settings. This means that their availability and quality is dependent on individuals, rather than as a consistently funded, integral part of a palliative care service (Trees, 2024).

Life Review and Legacy Work

Engaging in life review activities or legacy projects can provide individuals with opportunities to reflect on their lives, find meaning in their experiences, and leave behind a meaningful legacy. Access to such programs remains limited (Trees, 2024).

Although a substantial proportion of dying patients attest to the importance of addressing the spiritual, existential, and emotional facets of dying (Steinhauser et al., 2000), many have reported that medical care inadequately addresses these increasingly prominent concerns (Balboni et al., 2007).

The lack of effective interventions to treat existential distress is a critical shortcoming in the care of patients with advanced cancer and other serious and life-limiting medical illnesses and represents a high unmet need in medicine and our society.

Dignity Therapy

Dignity Therapy is a novel psychotherapeutic intervention designed to address existential and psychosocial distress in people who are terminally ill. It aims to improve their quality of life by guiding them through an interview, which invites them to share memories and express their thoughts, feelings and values; talk about their life accomplishments, their hopes and dreams for loved ones and how they wish to be remembered. This therapeutic interview results in the creation of a generativity document, which the patient is given to bequeath to friends or family. This can promote dignity towards the end of life, enhance spiritual and psychological well-being, mitigate suffering and engender meaning and hope. For family survivors, Dignity Therapy can help ease bereavement, by providing a document that expresses the feelings and thoughts of their departed loved one (Kissane, D, 2011).

5) The Limits of Palliative Care

While palliative care accommodates the needs of the majority of dying people, even the best-resourced care cannot relieve the extreme suffering some endure. Western medicine gives us many valuable gifts, but a model of death that only addresses the body, and ignores the very real experiences of the soul, is missing half the picture.

Regardless of resources, there are clear limits to the effectiveness of palliative care. This fact is acknowledged universally by responsible organisations and professionals involved in palliative care services. Palliative Care Australia put it this way "While pain and other symptoms can be helped, complete relief of suffering is not always possible, even with optimal palliative care" (Palliative Care Australia, 2006).

Experts put the number of patients truly beyond the help of Palliative Care at about 15%. As recorded in the Voluntary Assisted Dying debate in multiple Australian parliamentary enquires, a person's suffering can be savage, both intense and sustained. In 2016, 70% of respondents to an Australian Medical Association (AMA) survey agreed with the statement that: Palliative care and medical treatment cannot adequately alleviate the suffering of some patients (Australian Medical Association, 2016).

Despite Australia having the second-highest ranked palliative care system in the world, these responses reflect the reality of modern medicine: it can keep us alive longer, but still has no cure for illnesses like certain cancers and motor neuron disease, or treatment for the existential distress that often accompanies life-limiting illness (Economist, 2015).

“Even if good, modern palliative care was available for each and every terminally ill patient − we would still have the nightmares” – Clive Deverall, Founder of Palliative Care WA, quoted by Noreen Fynn, his widow (2017).

6) The Synergies between Palliative Care and Psychedelics

There is a shared history and overlap between the goals and philosophies of palliative care and the medical use of psychedelics. The hospice and palliative care movement came out of the work of Dame Cicely Saunders in the UK in the 1960s, and in the 1970s in Australia. This was the same time that psychedelic research into LSD and death-related anxiety was happening (Kast, 1966; Pahnke, 1969).

In the interview Palliative care and psychedelics: 5 Questions for physician Rachel Rackow, (2024) Rackow states “Both fields also incorporate humanistic principles: trying to improve the experience of dying, which is a human experience, not a medical experience. Tending to the personal and social domains that are inherent to the human experience, and going beyond just treating someone's pain or biomedical needs — that’s something psychedelics and palliative care share. One of the goals of people seeking psychedelic experience is to be able to change their perspective in order to be able to have a better quality of life and that's really what palliative care is about, too.”

Bunn and colleagues (2023) also discuss the similar values of palliative care and PAT: “There is something very clinical about antidepressants, it’s about restoring depressed mood to euthymia whereas actually a big bit of palliative care is helping people to find meaning at the end of their lives, to contextualise their lives, to retain hope up until death, to transcend the finitude of their deteriorating bodies and the mystical, spiritual, unifying benefits of psychedelics are unique to that class of medications/medicines, which antidepressants or other drugs don’t really have. So, I think for the holistic model of psychological and spiritual care that palliative care tries to foster, it really fits well with the ethos”.

PAT and palliative care share common goals and principles centred on holistic well-being and the alleviation of suffering, making a strong case for their integration. Both approaches aim to improve the experience of dying, which is a human condition, not only a medical one. PAT offers a unique therapeutic modality that can complement traditional palliative care interventions by addressing psychological and spiritual dimensions often overlooked in conventional treatments. Providing individuals with opportunities for profound healing, insight, and acceptance, PAT can enhance the quality of life for those facing terminal illness, promoting a sense of meaning, connection, and peace in the face of mortality. Integrating PAT into palliative care would offer patients a more comprehensive and personalised approach to end-of-life care, aligning with the overarching philosophy of palliative care to honour the dignity and autonomy of each individual throughout their journey.

In addition to the clinical trial evidence and patient testimonials, there is a growing body of professional endorsements for the use of psilocybin-assisted therapy in palliative contexts. Recent literature shows a notable rise in the acceptance of psilocybin-assisted therapies across multiple care settings, reflecting growing confidence in their clinical utility (Hearn et al., 2021; Page et al., 2021; Niles et al., 2021; Reynolds et al., 2021; Meyer et al., 2022). For instance, a survey of psychiatrists and psychologists in the United States reported that most psychiatrists anticipate a clear therapeutic role for psilocybin and related substances, with strong support for federally funded research (Barnett et al., 2018). A similar trend appears in the NHS, where more than three-quarters of psychiatrists polled acknowledged psychedelics' likely place in clinical practice (Page et al., 2021). Educational activities encompassing supervision, specialised training, and expanded knowledge seem to further enhance clinicians' readiness to adopt these treatments (Davis et al., 2022; Hearn et al., 2022; Barrnett et al., 2021).

In the palliative care domain specifically, professionals increasingly recognise that conventional, purely medical approaches may fall short, particularly for individuals experiencing existential distress (Voeuk et al., 2017; Ross et al., 2022). A series of qualitative interviews conducted with 19 palliative care professionals in the United States highlighted a receptiveness to psychedelic-assisted therapy as a new tool for addressing intractable spiritual or existential suffering (Niles et al., 2021). This perspective aligns with findings from practitioners who specialise in advanced cancer care (Reynolds et al., 2021; Ross et al., 2022), as well as those treating other severe life-limiting conditions (Beaussant, 2021). Collectively, these endorsements underscore a broadening consensus that psilocybin-assisted therapy could fill an important gap in end-of-life care, complementing established palliative interventions and offering a more holistic approach to existential distress.

Switzerland provides a compelling illustration of how psychedelic-assisted therapy (PAT) can align with the goals and practices of palliative care. Since 2014, psychiatrists, oncologists, general practitioners and palliative care physicians in Switzerland have been able to employ psilocybin (and other psychedelics, including LSD) under special exemptions granted by the Swiss Federal Office of Public Health (FOPH) (Aicher et al., 2024; Aicher & Gasser, 2024). Building on the nation's historic relationship with psychedelic research, most famously Albert Hofmann's discovery of LSD in 1943, Swiss clinicians have integrated psychedelics into limited medical use frameworks to relieve existential suffering in patients with serious and life-threatening conditions. This approach underscores the potential synergy between palliative care's holistic model of support and the transformative effects of psilocybin,

particularly when standard interventions cannot adequately address profound psychological or spiritual distress.

7) Psychedelic Assisted Therapy (PAT) Towards the End of Life: an Evolving Landscape

"Yeah, I definitely had like some fear taken, like taken off my shoulders. And really believing that, you know, my prognosis isn't going to be my reality and really, really believing that."

"But I think the shift in consciousness that comes from this medicine allows you to realise you have the choice to live your life, you know."

The above quotes from James Bunn's report, *Taboo to Treatment*, highlight the profound emotional and psychological relief that psilocybin-assisted therapy can offer individuals facing end-of-life challenges. They illustrate a shift away from dread and hopelessness toward a renewed sense of presence, reconnection with loved ones and the realisation that one can still exercise choice in how to live, even in the context of a terminal diagnosis. These firsthand testimonies underscore the potential of psychedelic-assisted therapy to address existential distress in a way that standard palliative care interventions often cannot.

PAT is a burgeoning treatment with growing interest across a variety of settings and disciplines. Empirical evidence supports PAT as a novel therapeutic approach that provides safe and effective treatment for people suffering from a variety of diagnoses, including existential distress at end of life. This approach has the potential to produce a paradigm shift in the psychological and existential care of patients with terminal illness. A welcome reprieve when we consider the limits of palliative care and its current treatment modalities (J. Trees and J. Topfer, personal communication, 2024)

Studies have shown that PAT can help patients facing end-of-life issues experience a reduction in anxiety, depression, and existential distress (Agin-Liebes et al., 2020), as well as an increased sense of meaning, interconnectedness, and acceptance of death (Shnayder et al., 2022). The profound mystical experiences induced by psilocybin have been reported to facilitate emotional processing, encouraging spiritual insights and personal transformation (Griffiths et al., 2016).

Despite its current label as a novel therapy Psilocybin has been used for centuries by Indigenous cultures for spiritual and healing purposes. Indigenous ceremonies involving plant medicines like Peyote and San Pedro often aim to help individuals face and accept significant life transitions—akin to modern palliative care objectives (MUD\WTR, 2024). These cultures often view psychedelic experiences as a means of connecting with nature, ancestors, and the divine as well as facilitating personal growth and healing. But Indigenous people are good sharers. A key reason researchers and patients outside of Indigenous communities can access psilocybin therapy is because Mazatec people in Mexico developed medicinal and sacramental uses of this mushroom. Shaman and wise woman, Maria Sabina then shared their knowledge with a U.S. ethnomycologist Gordon Wasson who wrote about his experiences in an article in Life magazine in 1957(Cornelius, 2023). Similarly, ancient cultures worldwide have employed psychoactive substances in rites of passage and healing

rituals, often framed as “little deaths” marking a major life transition (MUD\WTR, 2024). For example, the Wixáritari (Huichol) and Andean practitioners historically used Peyote and San Pedro cacti to help individuals let go of the past and move forward into their next phase. These practices share remarkable parallels with modern palliative care goals, offering psychological and spiritual support at critical life thresholds.

According to the article From Taboo to Treatment: The Case for Compassionate Access to Psilocybin in the UK (Drug Science, 2023), alleviating pain and existential anxiety in terminal patients was among the first proposed clinical uses of psychedelics, with several studies in the 1960s and 70s finding that they could induce profound mystical experiences and alleviate anxiety, depression, and existential distress in terminally ill patients. (Kast, 1964; 1966; Pahnke 1966; Grof et al., 1973; Richards et al., 1977).

The concept of using psychedelics for existential distress in end-of-life was introduced by British author Aldous Huxley in 1963, who was given lysergic acid diethylamide (LSD) on his deathbed to die peacefully (8). Subsequently, the landmark Kast LSD study examined the analgesic effects of LSD compared to traditional pain medications . The study suggested efficacy in pain reduction and patients reported decreased fear of death (15). Grof further evaluated LSD-assisted psychotherapy in open-label research in patients with terminal cancer. He reported up to a 70% improvement in depression, anxiety, and fear of death (16). Unfortunately, studies from this early era of psychedelic research had significant limitations in study design, including lack of controls and blinding (17).

The escalating recreational use of psychedelics in the 1970s, along with their association with counterculture, led to controversy, sensationalism, and ultimately, a ban on these substances (Griffiths et al., 2016; Johnson & Griffiths, 2017). Psilocybin’s classification as a Schedule I controlled substance in the United States, severely limited research opportunities, in the context of President Richard Nixon’s ‘War on Drugs’ in 1971. These significant regulatory barriers and the withdrawal of USA federal research funds meant all scientific studies were gradually discontinued (Johnson et al., 2008). Australia followed Nixon’s lead.

Psychedelic research in the U.S. restarted in the 1990s and has since offered specific new insights into the efficacy of psilocybin for several domains relevant to the care of the palliative patient: psycho-emotional distress and pain, cognitive health and the spiritual distress faced with a life-limiting illness. In 2018 Dr. Ira Byock MD, FAAHPM (Fellow of the American Academy of Hospice and Palliative Medicine) commented that “Given the prevalence of persistent suffering and growing acceptance of physician-hastened death as a medical response, it is time to revisit the legitimate therapeutic use of psychedelics” (Byock et al., 2018). Advances in neuroscience (including the use of functional MRI), changes in public attitudes and a growing body of research supporting their safety and efficacy have contributed to a global resurgence in understanding the therapeutic potential of psychedelics. In July 2023 the Australian Therapeutic Goods Administration (TGA) made the seminal decision to reschedule psilocybin as a Schedule 8 controlled medicine. Prescription is permitted by psychiatrists who have become authorised prescribers for this purpose under the TGA’s authorised prescriber scheme and as part of psychotherapy in medically controlled environments for Treatment Resistant Depression (TRD). This decision arose

from a robust evidenced base and extensive public consultation. MDMA was also re-scheduled for the treatment of post-traumatic stress disorder (PTSD). Across the gamut of mental health issues the research into psychedelic assisted therapy is resoundingly favourable. An area of urgent need.

International models further strengthen the case for PAT. Canada has taken steps toward legal access to psilocybin for terminally ill patients. According to TheraPsil, a Canadian nonprofit, single-dose psilocybin treatments have enabled some patients to reduce or discontinue opioids, reclaim meaningful time with loved ones, or, in some instances, make more informed end-of-life decisions (MUD\WTR, 2024). One patient, for example, chose to forego continued heavy opioid use and instead spent her final days laughing with loved ones before electing medical assistance in dying. Another patient was so deeply moved by psilocybin's therapeutic benefits that he decided life was still worth living despite physical suffering, an outcome described by family as "miraculous," though well-grounded in clinical science (MUD\WTR, 2024)

The recent Cochrane review by Schipper et al., (2024) concludes that the evidence for psychedelic-assisted therapy in treating anxiety, depression and existential distress in life-threatening diseases is of "low to very low certainty." However, this conclusion is primarily a reflection of the inherent challenges of researching terminally ill populations. Studies in this area are constrained by small sample sizes, significant ethical challenges and difficulties in achieving robust blinding, all of which limit the certainty of traditional randomised controlled trials in this vulnerable group. These methodological issues do not imply that psilocybin is ineffective; rather, they highlight the limitations of conventional trial designs when applied to palliative care settings. In contrast, recent Phase 2 and Phase 3 studies, along with successful international compassionate-use programs in Switzerland, Oregon, and Canada have produced compelling safety and efficacy data. These studies demonstrate that psilocybin-assisted therapy can significantly alleviate existential distress, depression and anxiety among patients nearing the end of life, offering transformative benefits that are not captured by the narrow scope of the review. Moreover, real-world evidence from programs like TheraPsil in Canada shows that even a single dose of psilocybin can lead to substantial improvements in quality of life and reductions in reliance on opioids and other medications.

Based on the available evidence, a decision to reschedule the use of psilocybin for palliative care will revolutionise treatment paradigms and improve patient outcomes exponentially beyond what traditional psychiatry has been able to offer. A profound change in a person's relationship with death is characteristic of a guided psychedelic experience (Harris, 2023). The need for a treatment such as PAT, that is, an evidence-based, potentially curative treatment, including for existential distress towards the end of life, is clear. Using PAT to help bring about healing in people with life-limiting illnesses, including in the terminal phase of their lives, has a profoundly positive ripple effect from the patient to those that care for them, across friends and families, throughout communities and through generations (Topfer and Trees, 2024).

8) Psychedelic Assisted Therapy (PAT) at End of Life (EOL) is an Ethical Imperative

It's not about pain, it's about suffering.

Suffering is an intensely personal experience and is not confined to physical pain. Palliative care clinicians and teams also encounter patients whose misery is rooted in emotional, social, existential and/or spiritual distress. Cancer, heart failure, liver failure, and motor neuron disease are among the life-limiting diseases that often result in a cascade of personal losses: independence, including in self-care, a sense of contributing to others lives, loss of enjoyment, meaning and purpose. Ultimately, some ill people say they have lost any reason to go on living.

People suffering life-limiting illnesses experience symptoms that are challenging to assess, treat and manage — even with the best palliative care. This is widely acknowledged, including by Palliative Care Australia and the Australian Medical Association in the VAD report, State of VAD, Voluntary Assisted Dying in Australia & New Zealand (Go Gentle, 2024).

One common theme in palliative care is the desire to preserve as much autonomy and choice as possible for those approaching death. Recent anecdotal evidence from organisations like TheraPsil (Canadian nonprofit) suggests that psilocybin-assisted therapy can help patients take a more active role in their final journey, whether that involves spending pain-free time with loved ones, making a confident decision about MAiD, or reframing one's relationship with death itself (MUD\WTR, 2024).

We have a real gap in our therapeutic armamentarium for treating patients with terminal illness with existential distress, anxiety and depression, and a lot of people die with preventable torment. Based on trials to date, if psilocybin-assisted therapy was available, we could prevent a lot of suffering in a significant number, perhaps even a majority of patients. Where palliative care falls short in its ability to treat existential distress, PAT at end of life offer the probability of meeting this clinical need.

A person should have the right to decide about fundamentally important matters that affect him/her, and a humane society has a moral obligation to afford those who are suffering the right to choose a dignified end.

PAT is supported by a robust evidence base and ethical arguments that a civilised contemporary society cannot (and should not) ignore. Namely:

1) The Principal of Individual rights, autonomy and choice.

A cognitively competent individual should have self-determining choices about their dying process if this does not interfere with the rights of others.
As sovereign beings we are ethically entitled, and should have a legal right, to be protected from unnecessary suffering at the end of life.

Most patients who are facing terminal illness would like the option of whether to participate in PAT, should their existential distress be intolerable. In the same way that they can have

an elect to have an operation or elect to go down the palliative care route, they would like to have a choice (Wang, J et al, 2024).

2) PAT is a compassionate answer to pain, suffering and indignity.

Some people are suffering intolerably while dying. Creating a safe, legal pathway for accessing PAT towards EOL allows for more compassionate choices than our current laws permit. PAT is a merciful answer to insoluble pain, suffering and indignity in terminal illness.

When no other options are open to a person in the final stages of a terminal illness except perhaps voluntary assisted dying, a person suffering unrelenting pain and distress who consistently and rationally requests an end to their agony, needs a process whereby their dying wish can be granted.

Following a deontological moral reasoning perspective:
-Unnecessary suffering is evil and should be avoided.
-Human freedom should be respected when there is no substantial harm to others.
-Dignity (understood as self-worth or freedom from humiliation) should be protected and not violated by 'forcing' someone to 'endure' 'horrible' suffering.

3) An International Change

There is growing interest in the potential benefits of psilocybin-assisted therapy to treat existential distress towards the end of life in many parts of the world.

A recent Canadian study by Plourde and colleagues (2024) assessed the social acceptability (amongst the general public) of psilocybin-assisted therapy for existential distress at the end of life. The results were that "Overall, 79.3% of 2800 participants considered psilocybin-assisted therapy a reasonable medical choice for a patient suffering from existential distress at the end of life, 84.8% agreed that the public health system should cover the costs of the intervention and 63.3% would welcome the legalisation of psilocybin for medical purposes."

Healthcare Professionals also express an optimism and openness when it comes to PAT at EOL. In palliative care, specifically treating individuals experiencing existential distress, there is an increasing awareness among professionals that the current approaches are not adequate (Voeuk et al., 2017; Ross et al., 2022). Bunn and colleagues concluded "Based on semi-structured interviews conducted among 19 palliative care professionals in the United States, psychedelic-assisted therapies were recommended as a new approach to treating existential distress (Niles et al., 2021). This growing view corresponds with the attitudes of professionals who specialise in the provision of care to individuals with advanced cancer (Reynolds et al., 2021; Ross et al., 2022) as well as individuals diagnosed with other serious conditions (Beaussant, 2021)."

4) International Precedents

USA

On January 1, 2023, psilocybin services became legal in Oregon for individuals who meet the criteria set forth in the Oregon Psilocybin Services Act and outlined in the rules and

regulations that have been developed by the Oregon Health Authority (OHA). See attached document 'Guidance for Clinicians Working with Oregon Psilocybin Services and People with Advanced Illness' in Supporting Documents

This unprecedented legislation paved the way for Oregon Health & Science University's (OHSU) psilocybin services program, which began offering psilocybin-assisted therapy in January 2023, under the supervision of licensed facilitators ,for patients with depression and anxiety related to life-threatening illnesses.

A recent review by Bellman (2024) of Oregon's implementation highlight several key aspects of this pioneering framework:

- Comprehensive Regulatory Framework: The Oregon Psilocybin Services Act mandates that the OHA oversee the licensing, manufacturing, transportation and administration of psilocybin products. This ensures that only certified facilities and trained facilitators provide the therapy.
- Clinical Protocols and Patient Safety: Detailed guidance for clinicians includes robust patient screening, standardised dosing protocols (typically around 25 mg per session) and structured post-session integration support. These measures are designed to maximise therapeutic benefits while minimising risks.
- Operational Challenges and Lessons Learned: While the Oregon model shows promise, particularly in alleviating cancer-related depression and anxiety, it also faces challenges such as federal legal ambiguities, regulatory hurdles and the need for systematic data collection to refine best practices. These insights offer valuable lessons for other jurisdictions considering the integration of psilocybin-assisted therapy into clinical practice.

By setting these rigorous standards, Oregon not only establishes a precedent for safe and ethical psilocybin use in end-of-life care but also provides an evolving blueprint for international adoption of similar therapeutic models.

Canada

The 'Special Access Programme' of Health Canada has granted exemptions for certain individuals to use psilocybin for medical purposes, including palliative care.

A Case Study from Canada

The Canadian exemptions allow patients to possess and consume psilocybin under the supervision of healthcare professionals., such a patient was Thomas Hartle. Any person with stage four colon cancer deals with anxiety, but for the first few years after his diagnosis in 2016, Thomas Hartle considered himself to be managing. This was partly because his PET scans indicated the cancer wasn't progressing rapidly. That changed in 2019, when a colonoscopy found tumors on his large intestine that the scans missed. A follow-up surgery found dozens more. His relative calm evaporated. Hartle says of his experience "For days on end, I would sit alone, overwhelmed, in a darkened room. At other times, my anxiety was so crushing that I needed someone to accompany me at every moment. Maybe one of my intestines is going to rupture today, and I had to have somebody near me in case it does. In both of those cases, I wasn't being present for what was going on in my life". In 2020, Hartle had his first psilocybin session with TheraPsil's founder, the psychologist Bruce Tobin. He

felt himself disappear: an experience as close to death as one can have while still being alive, he said. After it was over, instead of being afraid of the inevitable outcome of his illness, he felt relief. “It gave me a taste of what life after life could be like,” he said. “Instead of the idea that the lights shut off, the party’s over, it was like a transition from one state to another. That was really comforting to me.” (The Guardian, 2024). See Appendix for Hartle’s letter in support of this application. (Hartle T, 2021).

See attached document ‘Hartle Letter’ in Supporting Documents

TheraPsil is a nonprofit organisation in Canada that provides legal and subsidised access to psilocybin for individuals with terminal illnesses. Since 2020, it has facilitated psilocybin treatments for end-of-life patients under Health Canada’s Special Access Program, reporting notable improvements in existential distress. TheraPsil’s success underscores the viability of incorporating psilocybin-assisted therapy into palliative care frameworks and aligns with our proposed model of licensed, medically supervised treatments.

One TheraPsil patient with advanced cancer reported:

“Psilocybin therapy lifted me out of constant fear, allowing me to cherish my final weeks with my family. I no longer felt defined by my diagnosis.”
This testimonial captures how even a single psilocybin session can alleviate profound existential anxiety and restore emotional well-being.

A 42-year-old mother nearing end of life described her psilocybin experience, facilitated by TheraPsil, as follows:

“Before psilocybin, I felt imprisoned by pain and an overwhelming dread of dying. Afterward, I found a sense of calm and acceptance. I could look my husband and children in the eye, and say that whatever happens, I feel at peace now.”
She subsequently reduced her reliance on opioid analgesics and reported a deeper engagement with her palliative care team.

Switzerland

Switzerland has been at the forefront of integrating psychedelic-assisted therapy (PAT) into palliative care, leveraging its unique regulatory environment and a longstanding tradition of psychedelic research. Since 2014, special exemptions for compassionate use have enabled Swiss clinicians, including psychiatrists, oncologists, general practitioners, neurologists, and palliative care specialists, to offer PAT as a means of alleviating profound suffering in patients with life-threatening and life-limiting conditions.

A comprehensive review by Aicher et al. (2024) details how the Swiss framework permits an interdisciplinary approach to PAT, ensuring that these therapies are delivered in controlled, supportive environments. This framework prioritises patient safety and emphasizes the integration of intensive preparatory and integration sessions alongside the psychedelic experience. Research in Switzerland has demonstrated that, when administered under stringent clinical protocols, substances such as psilocybin and LSD can yield rapid and lasting reductions in anxiety, depression, and existential distress among palliative care patients (Aicher et al., 2024).

The Swiss experience is rooted in a rich history with psychedelics. Albert Hofmann's discovery of LSD in 1943 laid the groundwork for decades of subsequent research. Although exploration of psychedelic medicine experienced a hiatus in the late 20th century, a pivotal letter to then-Minister Pascal Couchepin in 2006 rekindled scientific and clinical interest, catalysing a progressive regulatory landscape that now enables innovative research and compassionate clinical applications.

Switzerland has become a hub for clinical psychedelic research, with leading institutions exploring psilocybin therapy for patients facing life-threatening illnesses. For example, the psychopharmacology group at University Hospital Basel is internationally recognised for its work with psychedelics, and the hospital is currently hosting a Phase II trial investigating whether a single session of psilocybin-assisted therapy, combined with supportive psychotherapy, can alleviate severe, opioid-refractory pain in patients with advanced cancer. This innovative approach exemplifies the integration of palliative medicine and psychedelic therapy.

Furthermore, the Swiss model of PAT emphasises rigorous clinician training, standardised therapeutic protocols, and continuous outcome monitoring, all of which contribute to reduced risks and enhanced therapeutic efficacy. The integration of PAT into palliative care in Switzerland serves as a beacon for other nations considering similar approaches, offering valuable insights into how to safely and effectively incorporate psychedelics into mainstream medical practice.

Our Swiss colleagues have not only pioneered compassionate access models but have also fostered an environment of interdisciplinary collaboration that drives both research and clinical practice. Their efforts underscore the potential of PAT to transform end-of-life care, ensuring that even the most vulnerable patients are afforded a dignified and meaningful closure to their lives. This innovative work continues to shape the global dialogue on psychedelic medicine, offering a model of care that harmoniously blends scientific rigor with deep compassion for patients facing terminal illnesses.

See attached document in Supporting Documents written and signed by our Swiss colleagues advocating for the inclusion of Psilocybin in Schedule 8 for palliative care.

5) An Ageing Population

The global need for palliative care will continue to grow as a result of aging populations and the rising burden of noncommunicable diseases as well as some communicable diseases.

In their article, Expending perspectives on the potential for psychedelic-assisted therapies to improve the experience of aging (2022) physicians Yvan Beaussant and Kabir Nigam offer the perspective that PAT "may help society better care for older adults by changing the way we see and value aging, possibly shifting from a place of burden back to a place of wisdom, solidarity and respect, as is present in more traditional cultures."

Thus, psilocybin may have an indirect but crucial role in uplifting the societal and cultural foundations of palliative care, transforming what are held as possible outcomes for palliative and geriatric care.

6) Voluntary Assisted Dying (VAD)

Legalising PAT for existential distress in Australia is a compassionate and progressive step, especially in light of the existing legalisation of VAD across the six states. VAD provides relief to some of those facing terminal physical illness.

Existential distress often stems from a profound sense of meaninglessness, anxiety, or despair about life's purpose or one's place in the universe. Unlike physical ailments, existential distress may not have a clear medical solution, and traditional therapies often fall short in addressing its deep-seated roots.

PAT has shown promising results in clinical studies, facilitating profound existential insights and transformative experiences that can alleviate existential suffering. By legalising this therapy, Australia would offer a holistic approach to towards-the-end-of-life care, ensuring that individuals grappling with existential distress have access to treatments that honour their emotional and psychological needs.

Just as VAD respects individuals' autonomy and dignity in choosing the end of their physical suffering, legalising PAT acknowledges the importance of addressing existential pain with compassionate and innovative approaches. It opens doors to profound healing experiences that can bring solace and meaning to those navigating the existential complexities of life's end.

9) A Paradigm for Successful Dying

What would it take to die well? The rapid increase inmortality associated with the COVID-19 pandemic throughout the world underscored the importance of efforts to understand and improve what humans should experience at the end of their lives.

In a 2021 systematic review, Mehreen Zaman and colleagues reported on 11 conditions for a good death. These were, in order of frequency:

- Relief from physical pain and other physical symptoms;
- Effective communication and relationship with healthcare providers;
- Performance of cultural, religious, or other spiritual rituals;
- Relief from emotional distress or other forms of psychological stress;
- Autonomy with regards to treatment-related decision making;
- Dying at the preferred place, not prolonging life unnecessarily;
- Awareness of the deep significance of what is happening;
- Emotional support from family and friends;
- Not being a burden on anyone and
- The right to terminate one’s life.

Dr. Michael Ljuslin, Head of Clinic in theAcute Palliative Care Unit at the Geneva University Hospitals, recently presented his research regarding 'Themes of a good death or successful dying'. These include:

- Death process preferences;
- Pain free state;
- Emotional well-being (an opportunity to discuss the meaning of death);
- Family acceptance of death;
- Dignity;
- Completion of life (a life well lived, acceptance of one's own death);
- Religiosity/spirituality;
- Preference processing (autonomy regarding choices);
- Quality of life;
- Relations with health care and other end of life professionals.

Ljuslin's research echoes that of the systematic review. Again, with regard to a good death, PAT has the potential to enhance all of these aspects of successful dying. Reflecting on Ljuslin's and Zaman's research in light of the author's knowledge base, PAT is effective in addressing several of the conditions for a good death:

- Relief from physical pain and symptoms: Some studies suggest that psilocybin may help alleviate physical pain and symptoms associated with terminal illness, either directly or by reducing anxiety and existential distress, which can exacerbate physical discomfort.
- Relief from emotional distress and psychological stress: As discussed at length earlier in this document PAT has demonstrated potential in reducing anxiety, depression, and existential distress, which are common among individuals facing end-of-life issues. By facilitating profound psychological experiences, psychedelics may help individuals confront fears and find acceptance and peace, particularly in the care of appropriately trained health professionals.
- Enhanced communication and relationship with healthcare providers: PAT often involves intensive psychotherapy sessions before, during, and after the psychedelic experience. This therapeutic framework fosters deep introspection and facilitates open communication between patients and therapists, potentially improving the therapeutic relationship and enhancing trust and understanding.
- Cultural, religious, or spiritual rituals: Psychedelic experiences are often described as deeply spiritual or mystical, and they may facilitate profound spiritual insights and experiences of interconnectedness. For individuals with spiritual or religious beliefs, these experiences can be integrated into their end-of-life journey, providing solace and meaning.

Dr William Richards is a seminal figure within the field of psychedelic research; he has been working in psychedelic research since 1963.

"We've got to talk more about these transcendental or mystical states of consciousness. When they occur they seem to be the most powerful factor in attitudinal and behavioral change. Though every person's experience is unique, many reported new understandings of a religious or philosophical nature as well as helpful insights into their own lives and interpersonal relationships. They literally change the self-concept.

“Those who encountered mystical forms of consciousness frequently claim not only reductions in depression and anxiety, but also what you feel the nature of reality is, what the nature of the world is. There is often a loss of the fear of death, coupled with increased openness and curiosity about life. That’s powerful stuff.” (Richards, 2017)

Autonomy in treatment-related decision-making: PAT prioritises the autonomy and agency of the individual. By providing a supportive environment for exploring one's innermost thoughts and feelings, PAT can empower individuals to make informed decisions about their end-of-life care, including treatment choices and end-of-life planning.

Emotional support from family and friends: PAT can help individuals process unresolved emotional issues, reconcile relationships, and cultivate a sense of connection and empathy with loved ones. By addressing interpersonal dynamics and facilitating emotional healing, psychedelic therapy may strengthen familial bonds and provide a supportive network for individuals facing the end of life.

Awareness of the deep significance of what is happening: Psychedelic experiences often involve profound insights into the nature of existence, consciousness, and mortality. By facilitating experiences of awe, wonder, and interconnectedness, psychedelics may help individuals gain a deeper understanding and acceptance of their mortality, fostering a sense of meaning and purpose in the face of death.

10) Psychedelic Assisted Therapy: A Shifting Medical & Societal Paradigm

Appropriately addressing the needs of the human psyche in palliative and end-of-life care is a dynamic and emergent field. A significant subset of oncology and palliative care clinicians are seeking education, as they examine the mounting evidence demonstrating that psilocybin assisted therapy is a viable medical treatment. This awareness is being driven by large patient-led campaigns such as Project Solace by the Canadian charity, TheraPsil. Project Solace is the world's largest medical psilocybin access and data project. This project aims to expand legal access to psilocybin for patients in medical need, while developing a substantial body of evidence, using a real-world data registry.

Qualitative interviews with patients who have received psilocybin assisted therapy bring narrative richness to the numbers. For example, the following patient’s testimonial, used with her permission:

[...] "I had a huge smile on my face, and I burst out laughing — I had no idea why. It was such an overwhelming feeling, because with cancer there’s often not a lot of laughter, and not a lot of joy. Everything becomes so serious, all of the time. It was a powerful reminder that that joy was still there — and that I was still there [...]"

"[Later] something cracked open [...] the smaller release of sadness spiralling into the deep grief of it all. [...] I hadn’t even cried when I was diagnosed with cancer; I’d just carried on with life. But now, I was breaking down uncontrollably. One of the facilitators came and rested their hand gently on my chest. I took a deep breath, and just as suddenly

as it had come, the crying stopped. It was incredible. I hadn't known that I had had so much stored up [...]"

"The final, and perhaps strangest, part of the trip came next. I saw myself standing, talking to a shadowy version of myself and realised that that other self represented my cancer. I stood, facing it for a moment, then asked: "Why have you come back?" There was a pause, before I heard the response: that if the cancer hadn't come back, I wouldn't be here now, exploring these things. I asked what I should do with my life, and was told to exercise, eat good food, sing and dance."

"[...] I felt altered, immediately afterwards and in the months that followed. The messages I'd heard weren't rocket science — but it was as though, this time, they had come not from a therapist or a friend, but from somewhere inside me. [...] When I got home, I started making goals. The sense of my mortality quietened. My focus wasn't on dying any more — it was on living, and that was all I had wanted."

– 47-year-old woman with metastatic breast cancer, describing psilocybin assisted therapy

The remarkable success of PAT indicates that compassionate access as an option is essential for vulnerable patients who have exhausted other treatment options and are experiencing significant psychological distress.

Canadian research conducted to assess the social acceptability of PAT revealed that overall, 79.3% of 2800 respondents from four provinces considered psilocybin-assisted therapy a reasonable medical choice for a patient suffering from existential distress at the end of life. Further, 84.8% agreed that the public health system should cover the costs of the intervention and 63.3% would welcome the legalisation of psilocybin for medical purposes (Plourde et al., 2024).

Psilocybin's effects on depression, anxiety, and 'total pain' are particularly relevant in the context of life-limiting disease and end of life distress.

Palliative care physician, founder and director of the George Washington Institute for Spirituality and Health, Dr. Christina M Puchalski states, "… In the past few decades, physicians have attempted to balance their care by reclaiming medicine's more spiritual roots, recognising that until modern times spirituality was often linked with health care. Spiritual or compassionate care involves serving the whole person—the physical, emotional, social, and spiritual." (Puchalski, 2017).

11) Cost-Effectiveness and Healthcare Savings

End-of-life care represents a significant portion of Australia's healthcare spending. According to a 2021 analysis by Palliative Care Australia, hospital care for individuals in their final year of life can cost the system an estimated AUD 7.8 billion annually, with expenditures projected to rise as the population ages (Palliative Care Australia, 2021). Meanwhile, a Grattan Institute report suggests that better integration of community-based palliative care could reduce hospital admissions by up to 15%, potentially saving AUD 200

million each year (Duckett & Swerissen, 2014). By targeting existential distress, often a driver of unplanned hospital admissions—psilocybin-assisted therapy may help reduce some of these costs, particularly for patients who otherwise cycle in and out of acute settings due to unmanaged psychosocial suffering.

Against this backdrop, psilocybin-assisted therapy may yield further cost savings by alleviating existential distress, thereby lowering the frequency of crisis interventions, hospital admissions, and polypharmacy use in end-of-life care (Schenberg, 2018). Over time, incorporating psilocybin-assisted therapy into Medicare or the Pharmaceutical Benefits Scheme (PBS) would not only facilitate broader access and reimbursement but also help ensure that vulnerable patients receive comprehensive psychosocial support. Collaborations with cancer charities or end-of-life philanthropies could defray costs for eligible patients, expanding reach and promoting equity. Collectively, these steps align with public health goals of optimising quality of life while managing healthcare expenditures more effectively.

8. Toxicity information

8.1. If you have prepared a document with toxicity information, please upload your document as an attachment

Table 1
Acute Toxicity of Psilocybin

Species	**ROA**	**LD_{50}**
Mouse	IP	285 $mg.kg^{1}$
Rat	IP	280 $mg.kg^{1}$
Rabbit	IV	12.5 $mg.kg^{1}$

IP= Intraperitoneal. *IV= Intravenous*

8.2. Where data is available, we encourage you to provide the acute toxicity information in the Toxicity Table above and other toxicities under the relevant subheadings. If there is no data available, please indicate this with words to the effect of "no information" along with your justification as to why this should not hinder the scheduling consideration.

(a) Additional Information on Acute Toxicity

Animal Data (Non-Oral Routes)
Mouse (IP): LD_{50} = 285 mg/kg
Rat (IP): LD_{50} = 280 mg/kg
Rabbit (IV): LD_{50} = 12.5 mg/kg
(Passie et al., 2002; Gable, 2004)

Human Extrapolation
No formal oral LD_{50} data exist. However, an often-cited estimate suggests a potential lethal dose in humans of ~6 g—approximately 240 times a typical therapeutic dose (25 mg) (Gable, 2004). This figure is based on limited case reports and is not a direct LD_{50} determination. Because psilocybin is administered only a few times (often a single or double session) in a tightly supervised medical setting, formal LD_{50} data for oral use are of limited practical

relevance. Its observed safety in clinical trials indicates that the lack of an oral LD_{50} should not impede scheduling, given the low risk posed by therapeutic doses.

Clinical Context
In modern trials, psilocybin is administered orally at ~25 mg under strict medical supervision. No serious acute toxicity has been observed in this setting (Griffiths et al., 2016; Ross et al., 2016).

(b) Repeat-Dose Toxicity

Lack of Standard Studies
While some clinical trials have used multiple psilocybin sessions (e.g., a low-dose session followed by a high-dose session), this does not constitute a standard repeat-dose toxicity study (e.g., 28-day or 90-day protocols).
Psilocybin is generally administered infrequently (one or two sessions weeks apart), so the absence of formal repeat-dose data does not hinder scheduling. The dosing regimen in clinical practice simply does not align with typical long-term exposure patterns.

Clinical Use
Current clinical protocols use single-dose or two-dose sessions spaced weeks apart, limiting the relevance of repeat-dose toxicity in standard preclinical paradigms (Carhart-Harris et al., 2021; Davis et al., 2021).

(c) Genotoxicity

No Formal Genotoxicity Data
Although psilocybin has not undergone extensive genotoxicity testing, there is no evidence suggesting mutagenic or DNA-damaging effects at therapeutic doses.
Clinical and observational data show no safety signals pointing to genotoxic effects, and psilocybin's favorable safety profile in trials indicates that lack of explicit genotoxicity studies should not impede scheduling decisions.

(d) Carcinogenicity

No Evidence of Carcinogenic Risk
There are no long-term carcinogenicity studies specifically for psilocybin. However, no clinical or preclinical findings suggest tumorigenic effects at therapeutic doses.
Given the short and infrequent dosing regimen, there is minimal opportunity for carcinogenic processes to develop. The absence of such data does not pose a barrier to scheduling given psilocybin's established clinical safety record.

(e) Reproduction and Developmental Toxicity

No Known Data on Pregnant Populations
Clinical studies with psilocybin generally exclude pregnant individuals.
Because psilocybin is only administered in carefully supervised settings and typically restricted from use in pregnancy, the absence of specific reproductive toxicity data does not

hinder scheduling. Any future use in pregnant populations would require additional targeted research.

(f) Observation in Humans

Clinical Trials

Modern studies involving oral psilocybin at doses of 25–30 mg under controlled settings report mild and transient adverse events (e.g., headache, anxiety, transient blood pressure elevation) but no serious adverse reactions (Griffiths et al., 2016; Ross et al., 2016; Davis et al., 2021).

The TGA's Final Decision (February 2023) concluded that psilocybin has a favorable safety profile under medical supervision and poses minimal risk of dependence or abuse.

(g) International Regulations

Australia: The TGA rescheduled psilocybin to Schedule 8 for specific therapeutic indications (e.g., treatment-resistant depression) under strict Authorised Prescriber protocols (TGA, 2023).

Canada: Special Access Program (SAP) permits psilocybin for certain end-of-life or treatment-resistant cases.

United States: Investigational new drug (IND) pathway for research; Oregon has legalised psilocybin services under a regulated framework.

Switzerland: Psilocybin is controlled, but there is a pathway for compassionate use exemptions granted by the Federal Office of Public Health.

(h) Other Toxicity Information

Neurotoxicity

No clinical data indicate neurotoxic effects of psilocybin at therapeutic doses. Its pharmacological action and clinical trial outcomes support the position that it poses no meaningful neurotoxic threat under medical supervision.

Dependence / Abuse Potential

Observational and clinical trial data suggest low potential for misuse or compulsive use, especially when administered under strict clinical supervision (TGA, 2023).

9. Claims against the Scheduling Policy Framework (SPF) – scheduling factors

9.1. How does your proposed amendment align with the scheduling factors?

Our proposed amendment aligns strongly with the scheduling factors outlined in the Poisons Standard and the Scheduling Policy Framework.

First, psilocybin's favorable safety profile, characterised by very low acute toxicity, no significant neurotoxicity, and minimal potential for misuse when administered under controlled conditions, meets the risk-mitigation requirements of Schedule 8 controlled drugs. Clinical trials have consistently demonstrated that psilocybin, when given in a single

or few doses under strict medical supervision, produces transient and manageable adverse effects (Griffiths et al., 2016; Ross et al., 2016), supporting its safety for therapeutic use in a highly controlled environment.

Second, the significant body of evidence showing marked reductions in existential distress, depression, and anxiety among terminally ill patients underscores the pressing need for access to psilocybin-assisted therapy. From an ethical standpoint, failing to provide a potentially transformative treatment to individuals facing profound suffering at the end of life raises questions about the comprehensiveness of palliative care. In the words of one patient from James Bunn's Taboo to Treatment:

"I think her first words was you're back. I can see you. And so this person, who had been kind of distanced from her since the cancer diagnosis, that person wasn't there, and she felt like the person that she knew and was close to was present again. And I think that's the most profound thing is I think I was more. I am present now in my life. Umm, not in the dreads and fearful apprehension place that I just grown used to living."

Third, our proposal includes robust controls, such as restricted prescribing rights under the Authorised Prescriber scheme and targeted training requirements for palliative care specialists, that directly address the scheduling factors relating to minimising risks of misuse and ensuring safe, supervised administration. These measures further balance the substance's therapeutic potential with the appropriate level of regulatory oversight.

Finally, international regulatory experiences, including Canada, the United States and Switzerland, demonstrate that psilocybin can be safely integrated into clinical practice under rigorous oversight and monitoring. This global perspective, combined with the TGA's recent decision to reclassify psilocybin for therapeutic use (TGA, 2023), reaffirms our proposal's alignment with the scheduling factors regarding public health protection, clinical efficacy, and ethical responsiveness to end-of-life suffering.

In summary, our proposed amendment comprehensively meets the scheduling factors by balancing stringent public health safeguards with the critical need for a safe, effective treatment in end-of-life care. A substantial body of both domestic and international data demonstrates that psilocybin, when administered responsibly, effectively addresses the severe existential distress experienced by terminally ill patients.

We respectfully ask the TGA to consider the experience of individuals burdened not only by the physical weight of cancer or other life-limiting conditions, but also by the immense psychological suffering that often comes in one's final days. If we place ourselves in the shoes of a patient nearing the end of life, or imagine someone dear to us in that position, the potential for psilocybin-assisted therapy to provide comfort, acceptance, and dignity becomes strikingly evident. By expanding psilocybin's scope to include existential distress, we have the opportunity to offer transformative relief at a time when patients and families need it most.

Bibliography and supporting data

To:
The Secretary
Medicines Scheduling Unit
Therapeutic Goods Administration (TGA)
Canberra, ACT

1st August 2024

Advocacy for the Inclusion of Psilocybin in Schedule 8 for Palliative Care

We are writing on behalf of psychedelic therapists, researchers, and the palliative care community, originally spearheaded by Swiss professionals and joined by international supporters, to advocate for the expansion of the indications for psilocybin's classification in the Australian Poisons Standard as a Schedule 8 medicine to include existential distress towards end of life, such that it is available under the Authorized Prescriber Scheme. We also wish to advocate for the expansion of the eligibility of the TGA's Authorized Prescriber scheme to include physicians registered with the Australian Health Practitioner Agency who are Fellows of the Royal Australian College of Palliative Medicine and other physicians caring for patients towards end-of-life or working in a palliative care capacity.

This plea is founded on substantial and growing evidence demonstrating the efficacy and safety of psilocybin-assisted therapy in addressing the multifaceted psychological suffering experienced by patients with life-threatening illnesses.

The Swiss Perspective on Psychedelic-Assisted Therapy: In Switzerland, we have been at the forefront of integrating psychedelic-assisted therapy (PAT) into palliative care in the framework of limited medical use based on special exemptions from the Swiss health authority (Federal Office of Public Health, FOPH) since 2014. A comprehensive review of the framework of the Swiss PAT can be found in the recently published articles by Aicher et al. (2024), Aicher & Gasser (2024). This framework allows psychiatrists, oncologists, general practitioners, neurologists, and palliative care physicians to utilize these substances to alleviate suffering in patients with life-threatening or difficult-to-treat conditions. Switzerland has a rich history with psychedelics, starting with Albert Hofmann's discovery of lysergic acid diethylamide's (LSD) effects in 1943. The exploration of the medical applications of psychedelics resumed in 2006, following a pivotal letter to then-Minister Pascal Couchepin, which paved the way for research.

Patients in palliative care settings endure a significant burden of psychological distress, manifesting as depression, anxiety, demoralization, and physical symptoms including pain and others. These distressing psycho-existential symptoms often prove refractory to conventional treatments such as antidepressants and anxiolytics, leaving patients in profound suffering during their final days. Studies have consistently highlighted this treatment gap:

- **Depression and Anxiety:** Mitchell et al. (2011) reported that nearly 40% of patients in oncological, hematological, and palliative care settings suffer from mood disorders, including depression and anxiety, which are notoriously difficult to manage with traditional therapies. Vita et al. (2023) further confirmed the limited efficacy of antidepressants in oncological patients.

- **Demoralization:** Bovero et al. (2019) found that 30–70% of end-of-life cancer patients experience demoralization, a condition characterized by feelings of helplessness, hopelessness, and the wish for hastened death. This state of existential distress significantly impacts their quality of life and underscores the need for more effective interventions.

Recent clinical trials and systematic reviews (e.g., Schipper et al., 2022) have demonstrated that classical psychedelics like LSD- and psilocybin-assisted therapy offer a promising alternative to conventional treatments. Psilocybin, a naturally occurring psychedelic compound found in mushrooms, has shown robust efficacy in reducing psychological distress in palliative care patients:

Safety and Efficacy: Gasser et al. (2014) and Holze et al. (2023) reported that LSD-assisted psychotherapy significantly and safely reduced anxiety in patients with life-threatening diseases. Similarly, Griffiths et al. (2016), Grob et al. (2011), and Ross et al. (2016) found that psilocybin treatment produced substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer in a safe manner. Both found that psilocybin can also reduce demoralization.

Comprehensive Therapeutic Approach: In Switzerland, a transdiagnostic understanding of the effect mechanism of PAT (Kelly et al., 2021) underlies the current treatment practice. Psilocybin interventions are multidimensional, addressing not only primary outcomes such as symptoms of anxiety and depression but also improving secondary outcomes like demoralization, quality of life, death anxiety, spiritual well-being, and death transcendence. Agrawal et al. (2024) highlighted the feasibility and safety of psilocybin-assisted group therapy in patients with cancer diagnosed with major

depression, further emphasizing its potential in the palliative care context and highlighting the value of group settings for PAT (Gasser, 2021; Oehen & Gasser, 2022; Ponomarenko et al., 2023) and PAT in palliative care specifically.

Growing Recognition of PAT's Potential: The European Union's recent funding of the PSYPAL consortium highlights the increasing recognition of PAT's potential in palliative care indications. This initiative seeks to investigate the efficacy of psilocybin in treating psychological distress in patients with progressive, incurable illnesses such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), atypical Parkinson's disease (APD), and chronic obstructive pulmonary disease (COPD). Furthermore, there are at least seven other PAT trials currently being conducted in the field of palliative care including studies in Australia (Schipper et al., 2022).

Given the significant unmet needs of palliative care patients, which leaves a major burden on vulnerable patients unaddressed, and the compelling evidence supporting psilocybin's therapeutic benefits, we urge the TGA to consider expanding Schedule 8 to include psilocybin for end-of-life distress and to widen the scope of physicians eligible to purvey these treatments. This inclusion would not only address the profound suffering of these patients but also pave the way for more comprehensive and humane palliative care.

Thank you for your consideration.

Please do not hesitate to contact us if you have any questions or topics to discuss.

Sincerely,

Psychedelic and palliative care professionals

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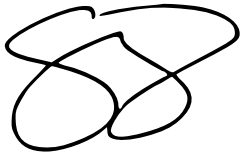

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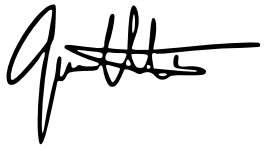

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Dear Sir/Madam,

This document includes endorsements from colleagues within the Swiss PAT team, along with signatures from internationally recognised experts who have worked with psilocybin-assisted therapy (PAT) for end-of-life existential distress. Their collective support further reinforces the growing clinical and research-based evidence advocating for psilocybin's therapeutic potential in alleviating existential distress and improving the quality of life for individuals in palliative care.

We hope you will consider this additional supporting documentation as further evidence of the strong professional and expert endorsement for the inclusion of psilocybin in Schedule 8 for palliative care.

Yours sincerely,

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DATE: Feb 28, 2021

First, I would like to say thank you for the opportunity to speak about my patient experience with you. My name is Thomas Hartle, and I am a Canadian who has been dealing with stage 4 colon cancer for the past 5 years. I have undergone a significant number of different treatments and therapies as part of my condition. These therapies include medical procedures, naturopathic procedures, and several natural supplements. I am the first person in Canada to legally use psilocybin to treat the anxiety I have experienced as a result of my terminal cancer.

What we are considering here is not a discussion of the recreational use of a drug, which is a completely different matter from the use of any drug in a controlled clinical setting with medical supervision. I'm including here a copy of the section 56 exemption that was granted to me by the Minister of health and the Office of Controlled Substances here in Canada so that you have an idea of the restrictions that are placed on the usage of psilocybin that ensure that safety is a primary concern.

Some of you may be familiar with the kind of devastating physical effects that having stage 4 cancer can cause, but like so many things concerning mental illness, we often do not speak about the mental and emotional toll that cancer also imparts. We seem to be more comfortable talking about topics like death than we are to address issues like anxiety. Mental health is somehow a taboo subject that makes people feel they are somehow weak or ashamed to seek help. My cancer has put me in a position where I simply do not have time left to ignore things the way that more healthy people are able to. When you have a terminal illness, hearing talk about studies that may (or may not) produce any outcome in 3 or more years' time is the equivalent of saying that nothing will be done for the rest of your life. Nothing will improve for the rest of your life. You will not get any relief from the anxiety or depression for the rest of your life, so every minute that you have left will likely be one where you are suffering. With a hopeless prognosis like this, it isn't surprising to find that many opt for suicide instead of the extended suffering that a lack of options guarantees. My personal experience is that this suffering can be alleviated effectively and with almost no side effects or risk.

For someone like myself, factors such as the small possibility for a negative reaction from a psychedelic such as psilocybin are trivial in the face of the absolute certainty that stage 4 cancer kills nearly everyone who has it, often within 18 months. Equally, as someone with a terminal diagnosis, I assure you that the possibility of experiencing some discomfort because of a "bad trip" is also almost laughable if you understand the level of daily discomfort cancer causes. This daily discomfort for me was greatly compounded by the anxiety I experienced over the uncertainty my life now has.

The most common question I am asked about my experience with psilocybin is usually concerning how a psychedelic substance could have any effect on something seemingly unrelated like anxiety. I can offer you the comparison of my experience between a traditional anti-depressant and psilocybin.

In a nutshell, the anti-depressant suppresses feelings for the duration that the drug is in effect. It removed the depths of negative feelings to some degree, but it also removed a proportionate amount of the peaks of happiness and wellbeing. Without the drug, everything returned to its original state with the same busy thoughts that are inherent to having anxiety and depression. The use of this drug is a lifetime commitment. For some, this is an acceptable option, but for me, it was not OK to trade the rest of my life with anxiety for the rest of my life feeling numb.

By comparison, the psilocybin gave me a different perspective on my circumstances. It did not only change the way I was feeling, but it also changed the way that I thought about what was happening to me. I have used psilocybin twice, and at this point, I don't feel any need to use it again. My results are typical, and as someone who has been extremely public about what most people would consider a personal matter, I have been approached by numerous people who have shared their experiences with me on the therapeutic use of this medicine. This perspective shift and the life changing result it has had for me is a theme that I have heard repeated by every patient I have spoken to. Every experience is different, and some are certainly challenging from an emotional point of view. We have anxiety because we are dealing with difficult things. Dealing with difficult things is not easy no matter what mode of treatment you take.

I will not try to tell you that this is somehow a cure all for mental illness. Of course, it isn't, and anyone who says so certainly does not understand how it works any more than someone who says that it has no medicinal value. Information on the toxicity of psilocybin is readily available, as are studies by highly reputable universities. There is a large body of research that is available from the 60s prior to the criminalization of the entire class of drugs. Many of the claims made against psilocybin such as its addictive potential are simply not supported by actual research. For myself, my doctors, and my government, this was sufficient to give me the opportunity to see if it would also work for me in the same way that it worked for 80% or people in the studies.

I am grateful that my government representatives were not only well informed, but also acted in a way that showed real human compassion. It would have been a simple matter for them to just say no and wait for me to die and no longer present a problem for them. Instead, they demonstrated that in medical matters, life changing medical decisions such as this are best left between a patient and their doctor. While the government in no way condones or promotes the use of psilocybin for any purpose, they had the decency to recognise that I am an informed and intelligent adult, capable of making choices about my treatment.

It is my hope that my positive treatment outcome, and the positive outcomes of others would be enough to convince you that the possibility of alleviating the suffering of the terminally is worth exploring. I would suggest that it could also be a mechanism to provide the research data that would show that this is in fact an effective treatment. Simply allow people who are terminally ill and who wish to use this treatment based on their own informed research to provide you with the evidence of their experience as recorded by their supervising medical practitioner. Allow them to use this medicine with protocols that have been established in other studies and treat that as your starting point in the development of protocols that reflect your own medical practices. If it does not deliver a result like I have experienced, they are no further behind than before they started. If they get even a fraction of the relief I have, you will give them at least the chance to be present with their loved ones instead their illness. There is nothing more precious to a family with a terminally ill member than quality time together.

Thank you for your consideration,

Thomas Hartle.

Guidance for Clinicians Working with Oregon Psilocybin Services and People with Advanced Illness

Current as of 10/17/23

Advanced Illness Coalition of Oregon: Daniel Abrahamson, Stephanie Barss PMHNP-BC, FNP-BC, Barb Hansen, Amy Koehlinger PhD, Angelique Loscar MBA, Rachel Rackow MD, MPH

Background

Psilocybin Services in Oregon

On January 1, 2023, psilocybin services became legal in Oregon for individuals who meet the criteria set forth in the Oregon Psilocybin Services Act and outlined in the rules and regulations that have been developed by the Oregon Health Authority (OHA).

How Psilocybin Services are Accessed

Oregon is the first state in the nation to approve a novel approach that is both non-prescriptive and non-medical in nature. Oregon's program differs from psychedelic assisted therapy (PAT) seen in most clinical trial protocols where one or more licensed health professionals are present with the participants during the session and, in some contexts, play a role in treatment and recovery. In Oregon, unlike cannabis's retail model where products can be purchased in a store and consumed at home, psilocybin may only be administered by a licensed facilitator in a licensed service center. An overview of the law and the process can be found here. Additional detail on the three components of Oregon's psilocybin services program (preparation, administration and integration) is provided in Appendix A.

Note: for consistency and clarity, we use the term "patient" when referencing an individual's relationship with a clinician and "participant" when referencing an individual's relationship with the psilocybin services program.

Rationale for this Guidance

Research from multiple institutions including Johns Hopkins University has shown that psilocybin-assisted therapy produces substantial and sustained decreases in depression and anxiety in patients with advanced illness. Because of this, Oregonians living with advanced illness may begin to seek information and guidance from their healthcare providers on psilocybin use to address end-of-life anxiety and depression. However, since in many cases this population has unique characteristics and needs (including, but not limited to, comorbid medical conditions, unwanted physical symptoms, and complex psychological symptoms such as existential distress, despair, anxiety, fear and confusion), these patient-provider discussions may benefit from additional considerations.

Purpose of this Guidance

This document is intended to serve as a guide to clinicians, especially those in palliative care and hospice, who work with people with advanced illness. The goal is to prepare clinicians to have these types of conversations, provide guidance to their patients and make appropriate referrals. Specifically, clinicians are encouraged to educate themselves on Oregon Psilocybin Services, know where to find the latest relevant clinical research, understand the pharmacology and potential drug interactions of psilocybin, have a sense of the contraindications and appreciate which patients might most benefit from a referral. While an in-depth review of the above is outside the scope of this guidance, references for additional education are provided below.

Furthermore, this guidance is intended to be used alongside the OHA rules and regulations. It should be noted that the Psilocybin Services Act does not promote psilocybin use as a treatment or therapy. Moreover, the OHA rules clearly define the scope of practice for facilitators as non-directive in nature. Psilocybin services do not require a referral or a prescription. Individuals interested in accessing psilocybin will contact a service center to begin the process. Facilitators will work with participants to determine eligibility based on OHA rules. However, not all facilitators will have experience working with individuals with advanced illness.

Evidence of Psilocybin Reducing Anxiety and Depression at End of Life

An overarching goal in palliative care is to positively impact the patient's quality of life with a focus on comfort. Clinicians are encouraged to review "Psilocybin in Palliative Care: An Update" (Whinkin, 2023) for an overview. There is evidence that psilocybin is safe and effective and provides psychological, social, and spiritual benefits. In particular, evidence suggests that psilocybin reduces feelings of anxiety, depression, and demoralization and improves openness and connectedness in individuals with cancer (Ross et al 2021, Griffiths et al 2016, Grob et al 2011, Rosa et al, 2022).

Guidance for Clinicians

The Role of the Clinician

As noted above, by law, psilocybin services may only be provided at OHA-licensed service centers by OHA-licensed facilitators. Given that, the role of the clinician is not to prescribe, obtain or administer psilocybin but rather to provide education, guidance, and, if appropriate, referrals.

Despite the fact that psilocybin remains a Schedule I drug federally, clinicians are strongly encouraged to be open to their patients' interest in psilocybin and to provide education, discuss risks and benefits and explore alternatives, as they would with any other intervention. It could be considered ethically inappropriate for a clinician to abandon a patient because of that patient's desire to access services under the Psilocybin Services Act.

Assessing Fit – Contraindications and Other Considerations

- By law, individuals under the age of 21, participants with a history of active psychosis or current thoughts of harming themselves or others, or those having taken the prescription drug lithium in the past thirty days are *ineligible* to receive psilocybin services.
- In addition to this, participants with any of the following may not be a good candidate for psilocybin services (these are not firm exclusionary requirements but rather considerations for more robust discussions between participants and their healthcare providers):
    - Palliative Performance Scale (PPS) < 50%
    - Do not feel psychologically, socially or physiologically stable
    - Unable to tolerate being at a service center for at least six hours
    - Are taking medications that require dosing during the administration session (for example, insulin or narcotics)
    - Psychiatric conditions judged to be incompatible with establishing rapport (examples include, but not limited to: Borderline Personality Disorder, Dissociative Disorder, Schizophrenia, uncontrolled Bipolar Disorder, active or recent psychosis or psychiatric hospitalizations)
    - First degree relative who meets criteria for Bipolar Disorder or Schizophrenia
    - Uncontrolled seizure disorder
- Other considerations include:
    - Currently taking investigational agents or monoamine oxidase (MAO) A or B inhibitors
    - Prescriber review of current medications and assessment for drug interactions including collaboration with the participants specialists and medical team as appropriate
    - Cardiac conditions including uncontrolled hypertension which may warrant monitoring during the administration session
    - Participants' prior experience and comfort level with psychedelics
    - Currently pregnant or lactating
    - Neurocognitive disorders
    - Limited stable housing or supportive relationships

Assessing Fit – Which Participants are "Good" Candidates for Psilocybin Services?

Facilitators are trained in assessing fit and will work with participants to determine if psilocybin services are right for them at this time. That said, "green flags" which suggest that a participant may be ready for psilocybin services include (but are not limited to):

- Has experience working with a therapist, counselor or coach
- Is open-minded and self-aware
- Has a strong support network

Encouraging a Collaborative Approach

Participants may benefit from a collaborative approach where multiple care providers and loved ones provide a support network for their psilocybin therapy experience. Such support may include, but is not limited to, licensed facilitators trained to work with medically complex individuals and their families or loved ones, as well as psychedelically informed medical providers, therapists, counselors, chaplains, coaches, and/or other specified meaningful support persons.

Additional considerations

Hype-Bubble

Increasingly, psychedelic therapy has received positive attention in the media. In a recent article published in the Journal of the American Medical Association Psychiatry, respected psychedelic researchers Roland Griffiths, David Yaden and James Potash suggest that the field is in the midst of a "hype-bubble" which could have negative ramifications for research and public perception if not addressed. Simply put, much is still unknown about psychedelics. Setting expectations with participants about the wide range of possible outcomes is critically important and strongly encouraged. This will be part of the facilitators' work, but clinicians will also have the opportunity to include this in their discussions with patients.

Insurance Coverage

Questions may arise as to insurance coverage of psilocybin sessions. Psilocybin services operate outside of the insurance system and are paid for out of pocket; however, participants may inquire about sliding scales or scholarships available from OHA-licensed service centers. Hospice agencies in Oregon will not include psilocybin on their formularies or cover the administrative session's cost, as the DEA lists psilocybin as a Schedule I drug and it is therefore not federally legal.

Considerations with Medical Aid in Dying (MAID)

As psilocybin awareness and use increase so might potential complexities related to pursuing or deciding not to follow through with medical aid in dying (Rosenbaum et al, 2023).

Valuable Resource

Clinicians are encouraged to read "Top Ten Tips Palliative Care Clinicians Should Know about Psychedelic-Assisted Therapy in the Context of Serious Illness" for an evidence-informed summary (Rosa, W. et al, 2022).

Evolution of This Document

This guidance is intended to be open sourced and adaptable to meet the needs of an individual participant's goals. It is intended to be used along with the related guidance for participants seeking psilocybin services in Oregon. As knowledge grows so will this guidance.

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Additional Resources

Informative Podcasts and Interviews

- Oprah Talks to Scientist Roland Griffiths About the Power of Psychedelics and the Gratitude of Mortality
- We Share the Cancer: Roland Griffiths and his wife, Marla, sit with Manish Agrawal to discuss how a stage IV cancer diagnosis has changed their lives
- Luminous: A Series About Psychedelics from 'To The Best Of Our Knowledge'
- We Can Do Hard Things with Glennon Doyle. Episode 240: Are Psychedelics an Answer? with Dr. Hillary McBride
- Psychedelic Therapy Frontiers
- Psychedelics Today
- The Tim Ferriss Show
- Trip on This
- Huberman Lab. Dr. Robin Carhart-Harris: The Science of Psychedelics for Mental Health

General Information

- OHA Psilocybin Services
- FDA Clinical Trials Database
- Heffter Research Institute
- Spirit Pharmacist
- Multidisciplinary Association for Psychedelic Studies (MAPS)

Appendix A

Additional Detail on the Preparation, Administration, and Integration Sessions

Per Oregon law, psilocybin can only be administered in an OHA-licensed service center by an OHA-licensed facilitator. While all service centers must meet minimum standards outlined in the OHA rules, they may offer different types of experiences such as location (urban vs rural), outdoor vs. indoor administration rooms, administration room setup, medical personnel on site, etc. The "set" and "setting" are thought to be important parts of a participant's experience and overall safety. Set is understood as the participant's mindset and expectation of the experience and outcomes, and the setting as the physical environment and relationships. While thought to be important, integration will also vary between service centers and facilitators.

An OHA-licensed facilitator must participate in at least one preparation session (in person or virtual) with the participant prior to administering the psilocybin. The next step is the administration session during which the psilocybin is taken, which is followed by an optional integration session (offered in person or virtual). The facilitator essentially functions as the participant's guide throughout the psilocybin experience with a primary goal of creating a safe and supportive environment. Given this, the participant-facilitator relationship is an important factor in ensuring a positive outcome.

Participants are encouraged to ask that there be coordination between their facilitator and trusted clinicians.

The psilocybin administration session may cause shifts, openness, and insights, and research suggests that long-lasting positive outcomes are more likely to occur when participants engage in ongoing integration work (Agin-Liebes et al, 2021, Watts el al, 2017). In general, the work is participant-led or from a place of "inner knowing" vs. a paternalistic and prescriptive approach (Clare, 2018). Integration or meaning- making after an administration session is not linear and can be enhanced and better understood with psychedelically-informed support. Outcomes from administration sessions are varied and unpredictable even in well-controlled and managed sessions. The experience and impact could be minimal/subtle, difficult/confusing, or worldview-changing and transformative. An interdisciplinary team, such as those found in palliative care, may play an important role in supporting the unfolding process.

Many people experience psilocybin sessions as spiritually meaningful, profound, or transformative. Participants may consider discussing their spiritual or faith background and worldview with their psilocybin services facilitator in the initial session to establish clear boundaries and expectations about how issues of transcendence, and spirituality that may emerge during psilocybin administration will be managed. Participants who have strong religious commitments may want to consult with a clergy member within their religious tradition to help process and integrate psilocybin experiences into their existing religious framework.

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Application to Expand the Application of Psilocybin in the Poisons Standard to Include Existential Distress Towards End of Life.

This document includes the tables mentioned in section 'Details claims against the requirements of the scheduling criteria' question 'What are the risks and benefits associated with the use of the substance?' of the TGA application

The Harbor-UCLA Study Exploring Psilocybin-Assisted Therapy for Anxiety in Patients with Advanced-Stage Cancer (Grob et al., 2011)

Figure 1 below for changes in State (A) and Trait (B) anxiety:

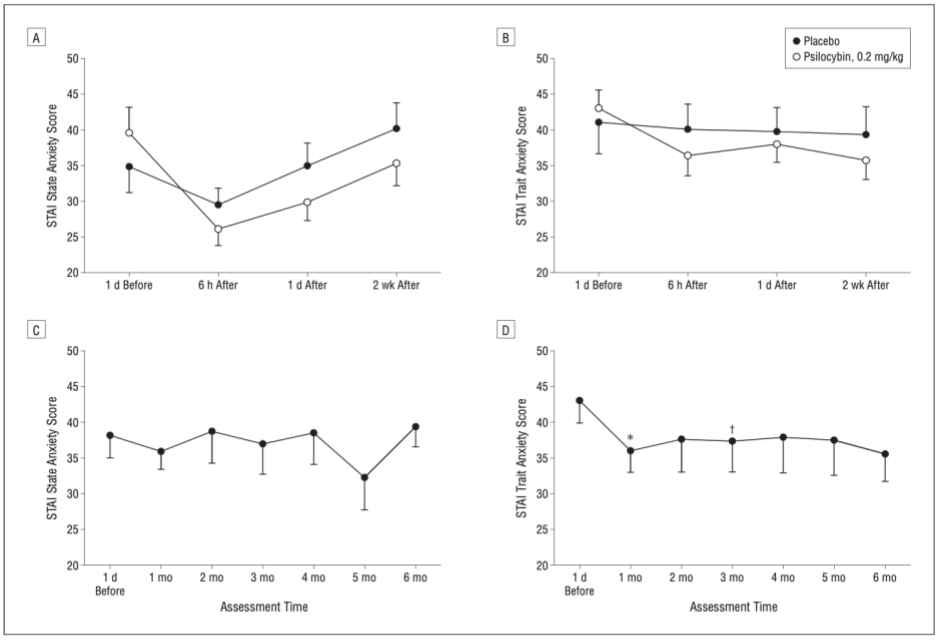


Figure 5. Mean (SEM) State-Trait Anxiety Index (STAI) state anxiety scores (A) and trait anxiety scores (B) 1 day before, 6 hours after, 1 day after, and 2 weeks after administration of psilocybin or niacin placebo are shown. Six months of mean (SEM) STAI state anxiety follow-up data (C) and trait anxiety follow-up data (D) are shown. The STAI was administered at monthly intervals for 6 months after the second treatment session, and the 6 sets of monthly follow-up data were compared with the scores obtained the first time the participants filled out the instruments (ie, 1 day before the first treatment session). *$P<.01$, †$P<.05$ for psilocybin vs the value from 1 day before the first treatment session (*t* tests were used to compare individual monthly follow-up values with values on the day before the first session).

Long-Term Follow-up of The NYU Psilocybin Trial for Treating Existential Distress in Cancer Patients (Agin-Liebes et al., 2020)

Table 1 demonstrated changes in depression and anxiety up to 4.5 years post-treatment

Table 2. Participant ratings on primary and secondary questionnaires.

Measure	Assessment time point			
	Baseline	6.5–8 months	3.2 years	4.5 years
HADS Anxiety	10.56 (0.93)	2.81 (0.95)[a]	5.50 (0.93)[a]	4.99 (0.98)[a]
HADS Depression	5.88 (0.71)	1.75 (0.73)[a]	2.25 (0.71)[a]	2.30 (0.75)[b]
HADS Total	16.45 (1.32)	4.38 (1.35)[a]	7.13 (1.32)[a]	7.34 (1.39)[a]
STAI State Anxiety	43.94 (2.51)	29.84 (2.58)[a]	33.00 (2.51)[b]	34.41 (2.67)[c]
STAI Trait Anxiety	47.81 (2.24)	28.23 (2.75)[a]	3.84 (2.85)[c]	35.78 (3.02)[b]
Beck Depression	14.19 (1.49)	5.09 (1.54)[a]	7.75 (1.49)[b]	5.45 (1.59)[a]

HADS: Hospital Anxiety and Depression Scale; SD: standard deviation; STAI: State-Trait Anxiety Inventory.
Data are means (SDs) collapsed across both dose sequence groups (N=16, N=15, N=15, N=14 at baseline, 6.5 months, mean 3.2 years and mean 4.5 years, respectively).
Supercripts indicate significant within-subject differences from baseline to time point ([a]$p<0.001$, [b]$p<0.01$, [c]$p<0.05$).

The Compass Pathways Phase 2 Trial Exploring Psilocybin-Assisted Group Therapy for Major Depressive Disorder in Cancer Patients (Agrawal et al., 2023)

Figure 2

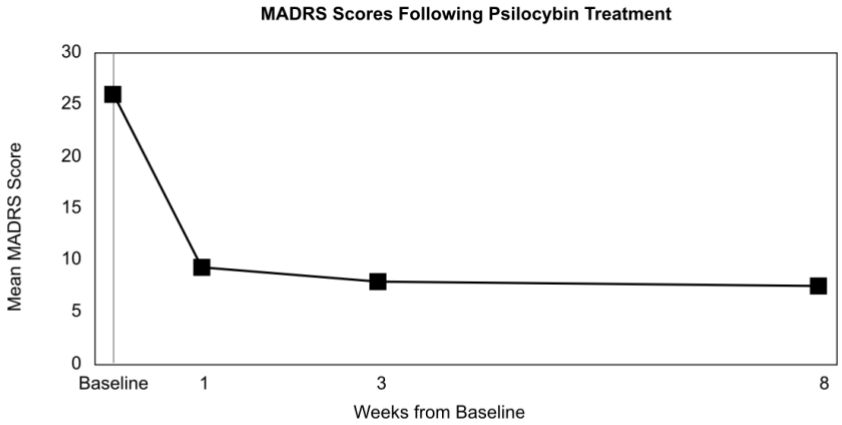


FIGURE 3 Mean MADRS Scores at baseline and weeks 1, 3, and 8 following psilocybin treatment. At week 1, change from baseline was −17.8 points (95% CI [−20.5 to −15,2]; $p < .001$), at week 3: −19.2 points (95% CI [−22.2 to −16.3]; $p < .001$), and at week 8: −19.1 points (95% CI [−22.3 to −16.0]; $p < .001$). MADRS indicates Montgomery-Asberg Depression Rating Scale.

Long-Term Follow-up of the NYU Trial (Agin-Liebes et al., 2020)

Table 2 below demonstrated changes in cancer-related demoralisation and hopelessness.

Table 2. Participant ratings on primary and secondary questionnaires.

Measure	Assessment time point			
	Baseline	6.5–8 months	3.2 years	4.5 years
Demoralization	31.88 (2.61)	16.84 (2.67)[a]	13.29 (2.69)[a]	14.32 (2.76)[a]
Hopelessness	5.75 (0.51)	1.65 (0.52)[a]	2.29 (0.52)[a]	1.65 (0.54)[a]

The COMPASS Pathways Phase 2 Trial (Agrawal et al., 2023)

Table 3 below demonstrated changes in cancer-related demoralisation.

TABLE 3 Efficacy measures at baseline and follow-up.

			Week 3				Week 8			
Measure	No.	Baseline	Change[a]	95% CI[a]	*p* value[a]	Cohen *d*	Change[a]	95% CI[1]	*p* value[a]	Cohen *d*
DS-II	30	14.5	−6.6	−8.8 to −4.5	<.001	1.04	−6.8	−9.1 to −4.4	<.001	1.02

Abbreviations: DS-II, Demoralization Scale II

Long-Term Follow-up of the NYU Trial (Agin-Liebes et al., 2020)

Table 4 below demonstrates changes in death anxiety up to 4.5 years post treatment.

Table 2. Participant ratings on primary and secondary questionnaires.

Measure	Assessment time point			
	Baseline	6.5–8 months	3.2 years	4.5 years
Death anxiety	8.06 (0.78)	6.09 (0.79)[b]	5.68 (0.79)[b]	5.75 (0.81)[c]

The COMPASS Pathways Phase 2 Trial (Agrawal et al., 2023)

Table 5 below demonstrates decreases in physical pain

TABLE 3 Efficacy measures at baseline and follow-up.

			Week 3				Week 8			
Measure	No.	Baseline	Change[a]	95% CI[a]	*p* value[a]	Cohen *d*	Change[a]	95% CI[1]	*p* value[a]	Cohen *d*
Pain VAS	30	3.5	−1.0	−.7 to −.3	.0050	0.45	−1.2	−2.0 to −0.4	.006	0.56

The COMPASS Pathways Phase 2 Trial (Agrawal et al., 2023)

Table 6 below demonstrates changes in existential distress

TABLE 3 Efficacy measures at baseline and follow-up.

			Week 3				Week 8			
Measure	No.	Baseline	Change[a]	95% CI[a]	*p* value[a]	Cohen *d*	Change[a]	95% CI[1]	*p* value[a]	Cohen *d*
SDS	30	11.2	−6.6	−9.1 to −4.0	<.001	1.0	−7.5	−9.6 to −5.3	<.001	1.19
EQ-5D-5 L	30	8.0	−2.0	−2.7 to −1.3	<.001	0.61	−2.3	−2.9 to −1.6	<.001	0.66

SDS, Sheehan Disability Scale EQ-5D-5 L, EuroQoL-5-dimension 5-level Scale;

The Compass Pathways randomised Phase 1 double-blind placebo- controlled healthy persons trial Table 7

Table 2. Most frequently reported TEAEs (occurring in >15% of participants in any treatment arm and ordered according to incidence in the 25 mg psilocybin arm) and summary of TEAEs of special interest (Safety Population).

	Psilocybin 25 mg (*N* = 30)		Psilocybin 10 mg (*N* = 30)		Placebo (*N* = 29)	
	n (%)	Events	*n* (%)	Events	*n* (%)	Events
Most frequently reported TEAE (MedDRA Preferred Term)						
Hallucination, visual	21 (70.0)	22	18 (60.0)	20	2 (6.9)	2
Illusion	18 (60.0)	26	19 (63.3)	25	4 (13.8)	5
Mood altered	15 (50.0)	25	13 (43.3)	23	6 (20.7)	9
Headache	15 (50.0)	16	9 (30.0)	12	5 (17.2)	5
Fatigue	8 (26.7)	8	9 (30.0)	10	3 (10.3)	3
Euphoric mood	7 (23.3)	8	7 (23.3)	7	0	0
Tension headache	6 (20.0)	6	3 (10.0)	3	3 (10.3)	3
Time perception altered	6 (20.0)	6	2 (6.7)	2	3 (10.3)	3
Emotional disorder	5 (16.7)	6	2 (6.7)	2	0	0
Somatic hallucination	5 (16.7)	6	8 (26.7)	8	4 (13.8)	5
Affect lability	3 (10.0)	3	5 (16.7)	5	1 (3.4)	1
TEAEs of special interest (MedDRA System Organ Class/Preferred Term)						
Any TEAE of special interest	26 (86.7)	80	25 (83.3)	81	10 (34.5)	19
Nervous system disorders	0	0	2 (6.7)	2	0	0
Memory impairment	0	0	1 (3.3)	1	0	0
Psychomotor skills impaired	0	0	1 (3.3)	1	0	0
Psychiatric disorders	26 (86.7)	80	25 (83.3)	79	10 (34.5)	19
Affect lability	3 (10.0)	3	5 (16.7)	5	1 (3.4)	1
Change in sustained attention	0	0	2 (6.7)	2	0	0
Depressed mood	2 (6.7)	2	1 (3.3)	1	1 (3.4)	1
Dissociative identity disorder	2 (6.7)	2	1 (3.3)	2	0	0
Euphoric mood	7 (23.3)	8	7 (23.3)	7	0	0
Hallucination[a]	2 (6.7)	2	3 (10.0)	3	0	0
Hallucination, auditory	4 (13.3)	4	4 (13.3)	4	1 (3.4)	1
Hallucination, gustatory	0	0	1 (3.3)	1	0	0
Hallucination, olfactory	1 (3.3)	1	1 (3.3)	1	0	0
Hallucination, tactile	4 (13.3)	4	2 (6.7)	2	0	0
Hallucination, visual	21 (70.0)	22	18 (60.0)	20	2 (6.9)	2
Mood altered	15 (50.0)	25	13 (43.3)	23	6 (20.7)	9
Somatic hallucination	5 (16.7)	6	8 (26.7)	8	4 (13.8)	5
Substance-induced psychotic disorder	1 (3.3)[b]	1	0	0	0	0

TEAEs were coded post hoc to MedDRA Version 21.0 Preferred Terms. TEAE: treatment-emergent adverse event; MedDRA: Medical Dictionary for Regulatory Activities.
[a]All TEAEs coded to the MedDRA preferred term 'Hallucination' were described as 'kinaesthetic hallucinations'.

Source: https://journals.sagepub.com/doi/pdf/10.1177/02698811211064720

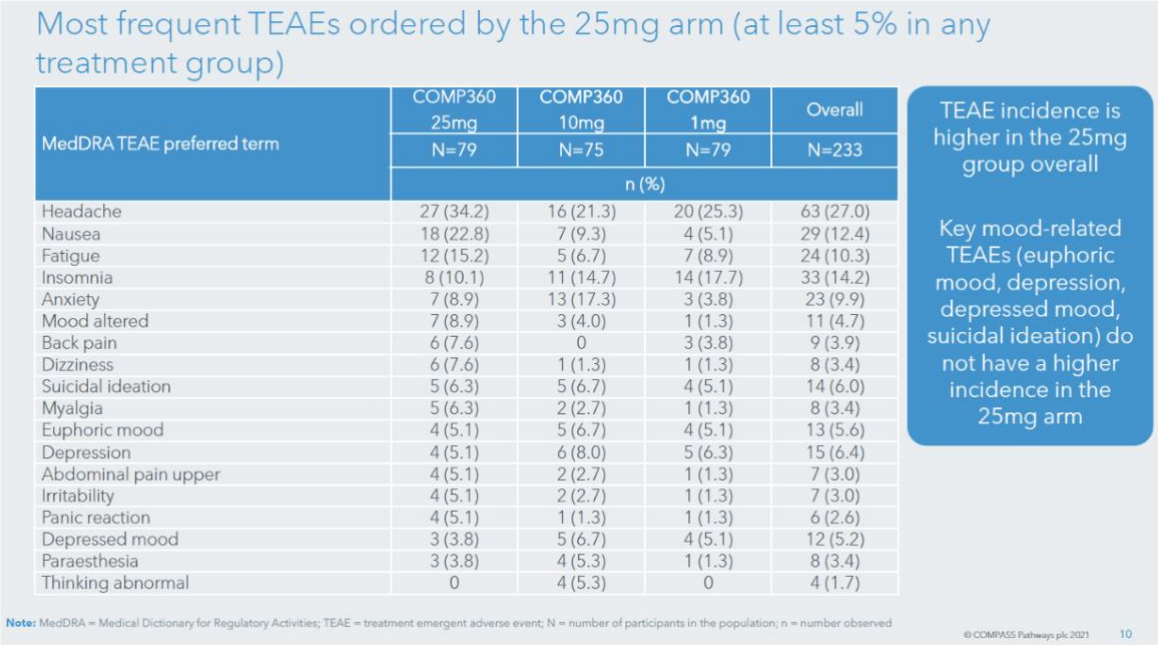
The Imperial College Phase 2 Trial comparing Psilocybin assisted psychotherapy with a leading SSRI plus therapy published in the New England Journal May 2021
Table 8

Table 4. Adverse events reported during the 6-week trial period and on dosing-day 1.

Event	6-Wk Trial Period		Dosing-Day 1	
	Psilocybin (N=30)	Escitalopram (N=29)	Psilocybin (N=30)	Escitalopram (N=29)
	number of patients (percent)			
Any adverse event	26 (87)	24 (83)	15 (50)	8 (28)
Serious adverse event	0	0	0	0
Related adverse event†	22 (73)	23 (79)	15 (50)	6 (21)
Adverse event reported in ≥3 patients during the full trial period				
Headache	20 (67)	15 (52)	13 (43)	5 (17)
Nausea	8 (27)	9 (31)	4 (13)	0
Fatigue	2 (7)	7 (24)	0	0
Anxiety	0	4 (14)	0	0
Dry mouth	0	4 (14)	0	0
Migraine	3 (10)	1 (3)	0	0
Palpitations	1 (3)	3 (10)	0	0
Sleep disorder	1 (3)	3 (10)	0	0
Diarrhea	1 (3)	2 (7)	0	0
Feeling abnormal	0	3 (10)	0	0
Feeling jittery	2 (7)	1 (3)	0	0
Vomiting	2 (7)	1 (3)	0	0

* These were the most prevalent adverse events that were reported during the trial.
† Whether an adverse event was related to the therapeutic intervention was determined by the study clinician through dialogue with each patient. Events deemed "probably" or "definitely" related were counted.

The Compass Pathways Phase 2b multi-site trial using psilocybin for treatment resistant depression released in November 2021
Table 9



Most frequent TEAEs ordered by the 25mg arm (at least 5% in any treatment group)

MedDRA TEAE preferred term	COMP360 25mg N=79	COMP360 10mg N=75	COMP360 1mg N=79	Overall N=233
	n (%)			
Headache	27 (34.2)	16 (21.3)	20 (25.3)	63 (27.0)
Nausea	18 (22.8)	7 (9.3)	4 (5.1)	29 (12.4)
Fatigue	12 (15.2)	5 (6.7)	7 (8.9)	24 (10.3)
Insomnia	8 (10.1)	11 (14.7)	14 (17.7)	33 (14.2)
Anxiety	7 (8.9)	13 (17.3)	3 (3.8)	23 (9.9)
Mood altered	7 (8.9)	3 (4.0)	1 (1.3)	11 (4.7)
Back pain	6 (7.6)	0	3 (3.8)	9 (3.9)
Dizziness	6 (7.6)	1 (1.3)	1 (1.3)	8 (3.4)
Suicidal ideation	5 (6.3)	5 (6.7)	4 (5.1)	14 (6.0)
Myalgia	5 (6.3)	2 (2.7)	1 (1.3)	8 (3.4)
Euphoric mood	4 (5.1)	5 (6.7)	4 (5.1)	13 (5.6)
Depression	4 (5.1)	6 (8.0)	5 (6.3)	15 (6.4)
Abdominal pain upper	4 (5.1)	2 (2.7)	1 (1.3)	7 (3.0)
Irritability	4 (5.1)	2 (2.7)	1 (1.3)	7 (3.0)
Panic reaction	4 (5.1)	1 (1.3)	1 (1.3)	6 (2.6)
Depressed mood	3 (3.8)	5 (6.7)	4 (5.1)	12 (5.2)
Paraesthesia	3 (3.8)	4 (5.3)	1 (1.3)	8 (3.4)
Thinking abnormal	0	4 (5.3)	0	4 (1.7)

TEAE incidence is higher in the 25mg group overall

Key mood-related TEAEs (euphoric mood, depression, depressed mood, suicidal ideation) do not have a higher incidence in the 25mg arm

Note: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event; N = number of participants in the population; n = number observed

 10

Usona Institute Randomised Clinical Trial Evaluating Repeated Doses of Psilocybin in Participants with Treatment Resistant Depression: Safety and Efficacy (Rosenblat et al., 2024)

Table 10

Adverse Event Category	Number of participants (%)
Appetite Disturbances	7 (23.3%)
Bladder Discomfort	1 (3.3%)
Blurred vision	3 (10%)
Bodily Pain/Tension	5 (16.7%)
Change in Bodily Sensation	2 (6.7%)
Cognitive Disturbance	1 (3.3%)
Dizziness	13 (43.3%)
Fatigue	9 (30%)
Hallucinations	2 (6.7%)
Headache	20 (66.7%)
Increased sweating	1 (3.3%)
Increased Respiratory Rate	1 (3.3%)
Irritability	1 (3.3%)
Lower Blood Pressure	1 (3.3%)
Muscle Convulsions	3 (10%)
Nausea	9 (30%)

Palpitation	2 (6.7%)
Panic Attack	1 (3.3%)
Persistent genital arousal, spontaneous orgasms	1 (3.3%)
Pre-syncope/Syncope	3 (10%)
Sleep Disturbances	5 (16.7%)
Stomach pain	3 (10%)

The Johns Hopkins Phase 2 Trial investigating psilocybin-assisted therapy for anxiety and depression exacerbated by a recent cancer diagnosis

Table 11

Table 3. Adverse events reported in Johns Hopkins study investigating psilocybin assisted therapy for anxiety and depression exacerbated by recent cancer diagnosis.

Adverse event description†	Low dose (*n* = 52)	High dose (*n* = 53)
Elevated Diastolic Blood Pressure (> 100)*	1 (2%)	7 (13%)
Elevated Systolic Blood Pressure (> 160)*	9 (17%)	18 (34%)
Elevated SBP (> 160) and/or DBP (> 100)	10 (19%)	18 (34)
Elevated Heart Rate (> 110)*	1 (2%)	3 (6%)
Mild Headache	0	1 (2%)
Nausea/vomiting	0	8 (15%)
Paranoia	0	1 (2%)
Psychological Discomfort	6 (12%)	17 (32%)
Physical Discomfort	4 (8%)	11(21%)
Anxiety during session	8 (15%)	14. (20%)

† In all cases, the adverse effect had resolved by the end of the session day.

* In one participant, the peak blood pressure magnitude (214/114 mmHg) met the protocol criterion for pharmacological treatment, however the protocol criterion for duration of elevation for pharmacological treatment was not met as the event lasted less than 15 minutes and returned to normal levels by the end of the session

The Compass Pathways Phase 2 Open-Label Trial Exploring Psilocybin-Assisted Group Therapy for Major Depressive Disorder in Cancer Patients: Adverse Effects and Safety

Table 12

TABLE 2 Adverse events reported by 10% or more patients and maximum severity.

			Maximum severity, No. (%)		
Event	*n*	%	Mild	Moderate	Severe
Any event	29	96.7	14 (46.7)	13 (43.3)	2 (6.7)
Headache	24	80	20 (66.7)	4 (13.3)	0
Nausea	12	40	11 (36.7)	1 (3.3)	0
Crying	8	26.7	8 (26.7)	0	0
Mood altered	8	26.7	7 (23.3)	1 (3.3)	0
Anxiety	7	23.3	3 (10)	4 (13.3)	0
Euphoric mood	7	23.3	7 (23.3)	0	0
Fatigue	7	23.3	5 (16.7)	2 (6.7)	0
Feeling of body temperature change	7	23.3	5 (16.7)	2 (6.7)	0
Insomnia	5	16.7	3 (10)	2 (6.7)	0
Yawning	5	16.7	5 (16.7)	0	0
Depressed mood	4	13.3	4 (13.3)	0	0
Paresthesia	4	13.3	3 (10)	1 (3.3)	0
Time perception altered	4	13.3	4 (13.3)	0	0
Dehydration	3	10	3 (10)	0	0
Depression	3	10	1 (3.3)	1 (3.3)	1 (3.3)
Illusion	3	10	3 (10)	0	0
Procedural pain	3	10	3 (10)	0	0
Psychomotor skills impaired	3	10	3 (10)	0	0
Rhinorrhea	3	10	3 (10)	0	0
Visual impairment	3	10	3 (10)	0	0
Palpitations	3	10	3 (10)	0	0

Source: https://acsjournals.onlinelibrary.wiley.com/doi/epdf/10.1002/cncr.35010

The University of Utah Pilot Study on Psilocybin-Assisted Group Therapy for Depression in Cancer Patients: Adverse Effects and Safety

Table 13

Table 2

Study-Related Adverse-Events

CTCAE Term	Grades 1-2	Grade 3	All Grades
Headache	3	0	3
Hypertension	0	1	1
Hypotension	1	0	1
Nausea	5	0	5
Ventricular tachycardia	1	0	1
Vomiting	1	0	1
Total patients affected	6	1	6
Total patients at risk	12	12	12

CTCAE = common terminology criteria for adverse events

Application to Expand the Application of Psilocybin in the Poisons Standard to Include Existential Distress Towards End of Life.

Registered Clinical Trials

#	Study Type	Condition	Start Year	Location	Sponsor	n	Psilocybin Dose	Control	Trial ID
1	Phase 2	Life-threatening illness, depression and anxiety	2020	Australia, VIC	St. Vincent's Hospital Melbourne	40	25 mg Psilocybin	100 mg Niacin (active placebo)	ACTRN12619001225101
2	Phase 2	Hospice Care Demoralisation	2022	US, Massachusetts	Yvan Beaussant	15	25 mg Psilocybin	None (open-label)	NCT04950608
3	Phase 2	Cancer Patients with Major Depressive Disorder	2020	US, Maryland	Maryland Oncology Hematology, PA	30	25 mg Psilocybin	None (open-label)	NCT04593563
4	Phase 1	Psychological distress and improve quality of life in patients with advanced pancreatic adenocarcinoma	2023	US, Nebraska	University of Nebraska	Still recruiting	25 mg Psilocybin	None (open-label pilot "Palliadelic" study)	NCT05220046
5	Phase 2	Anxiety/Depression in Stage IV Cancer	2022	US (NYU, multi-site)	NYU Grossman School of Medicine	~300	Single 25 mg session + psychotherapy	Placebo	NCT05398484
6	Phase 2	Demoralisation in Serious Illness (incl. cancer)	2023	US (California, multi-site)	Lundquist Institute at UCLA	~100	Psilocybin	None (open-label)	NCT05403086

#	Study Type	Condition	Start Year	Location	Sponsor	n	Psilocybin Dose	Control	Trial ID
7	Phase 2	Adjustment Disorder (existential distress) after advanced cancer diagnosis	2024	Australia (multi-site)	*Psyence Biomed* (Canada)	84 patients	25 mg, 10 mg, or 1 mg psilocybin (natural origin)	Active placebo (1 mg low-dose as control); three-arm, double-blind	ACTRN12624000449538p (ANZCTR)
8	Phase 1	Demoralised cancer survivors with chronic pain (palliative care context	2024	USA (Atlanta, GA)	Emory University (Winship Cancer Institute)	10 patients	Single psilocybin session (dose ~25 mg) under supportive care	None (open-label safety/feasibility trial)	NCT05506982
9	Phase 2	Depression and/or anxiety in participants who are being treated for advanced cancer	2024	USA (Texus)	M.D. Anderson Cancer Center	30 patients (estimated)	25mg Psilocybin	Participants will receive the placebo (100 mg of Niacin).	NCT06200155

#	Study Type	Condition	Start Year	Location	Sponsor	n	Psilocybin Dose	Control	Trial ID
10	Phase 1	Demoralisation Syndrome in Patients Diagnosed with Advanced Stage Cancer	2025	Canada (Ontario)	Gustavo Vazquez	15 patients (estimated)	25mg Psilocybin	**None** (open-label safety/feasibility trial)	NCT06818994
11	Phase 2	Patients Diagnosed with Advanced Stage Cancer	2024	Canada (Ontario)	University Health Network, Toronto	15 patients (estimated)	25mg Psilocybin	**None** (open-label safety/feasibility trial)	NCT06416085
12	Phase 1 Phase 2	Cancer-Related Anxiety in Patients With Metastatic Cancer	2023	University of Washington	USA (Washington)	55	Psilocybin	**n/a**	NCT05847686
13	Phase 2	Patients with Advanced Cancer	2024	Yvan Beaussant, MD, MSci	USA (Massachusetts)	15 (estimated)	Psilocybin	**None** (open-label safety/feasibility trial)	NCT06001749