Shroom Therapy
Use of Psilocybin in End of Life Anxiety Treatment

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Objectives

- Review end of life anxiety and American Society of Clinical Oncology treatment guidelines
- Outline the history and pharmacology of psilocybin
- Explore the physiological and psychological effects of psilocybin on healthy individuals
- Evaluate literature describing use of psilocybin for end of life anxiety
- Discuss future direction for treatment with hallucinogens
Patient Case

“I am so anxious that it is hard to think about anything else. I had lost my faith because of anxiety and it is terrifying.”

AL is a 53 year old woman with a diagnosis of metastatic ovarian cancer. Patient is currently receiving palliative treatment for pain and nausea. She has been suffering from anxiety and depression since her diagnosis 3 months ago.

Current medications:
Morphine ER 60mg daily
Morphine IR 10mg three times daily PRN
Ondansetron 4mg ODT every 8 hours PRN
Sertraline 150mg daily
Buspirone 20mg three times daily
Trazodone 150mg at bedtime
Alprazolam 0.5mg three times daily PRN
Gabapentin 800mg three times daily

Is this patient a good candidate for Psilocybin therapy?
End of Life Anxiety
End of Life

- End of life care – care for terminally ill patients focused on improving quality of life and making them more comfortable
- End of life emotions

- Fear
- Anger
- Guilt and regret
- Grief
- Anxiety
- Depression
- Feeling alone
- Seeking meaning

https://www.cancer.org
Epidemiology

- In palliative care, anxiety disorders affect approximately 10% of patients
  - More common in women, physically impaired, younger patients
  - Symptoms are reported by 25-48% of advanced cancer patients

- Multifactorial causes of anxiety
  - Treatment process
  - Disease progression
  - Uncontrolled pain
  - Dying
  - Uncertainty
All patients with cancer are evaluated for symptoms of depression and anxiety periodically across the trajectory of care.

- **7 item GAD-7**
  - **None/mild symptoms 0-4, 5-9**
    - Offer referral to supportive care services
  - **Moderate symptoms 10-14**
    - Psychosocial, Psychological interventions, ± Pharmacologic
  - **Severe symptoms 15-21**
    - CBT, Pharmacologic, combined

**Supportive Care**
- Psychological (individual)
- Pharmacological (SSRI, anxiolytics)
- Psychosocial (group)
Psilocybin Overview
Psilocybin History

- Isolated from Central American mushroom (*Psilocybe mexicana*) by a Swiss chemist Albert Hofmann in 1957
  - Found in many species of mushrooms worldwide
    - *Psilocybe*, *Conocybe*, *Gymnopus*, *Panaeolus*, and *Stropharia*
    - Along with peyote and dimethyltryptamine, psilocybin has a long history of ceremonial use
- Produced synthetically in 1958
  - Indocybin® Sandoz
    - Pure synthetic psilocybin
    - Marketed for experimental use
Psilocybin Pharmacology

- Hallucinogenic alkaloid
  - 4-phosphoryloxy-N,N-dimethyltryptamine
  - Similar chemical structure to serotonin

- Metabolized to 4 metabolites (psilocin, 4H1A, 41-IIAA, 41-IT)
  - Highly potent agonist at serotonin $5$-$HT_{2A}$
  - 50% oral absorption
  - Detectable in plasma in 20-40 min after oral administration
  - $T\frac{1}{2} = 163 \pm 64$ min with PO administration

- Considered 30x stronger than mescaline, 1/100-150 as potent as LSD
  - Strongly visual, less emotionally intense, less likely to result in paranoia

Addict Biol. 2002;7(4):357-64.
Physiological and Psychological Effects

- Eight healthy volunteers participated in a double-blind, placebo-controlled, dose-effect study

- Doses:
  - Very low dose (VLD) 45 mcg/kg
  - Low dose (LD) 115 mcg/kg
  - Medium dose (MD) 215 mcg/kg
  - High dose (HD) 315 mcg/kg

- BP, EKG, temperature, neuroendocrine data, blood chemistry

- Global Altered State of Consciousness Score

Addict Biol. 2002;7(4):357-64.
Physiological Effects

- **EKG**
  - No evidence of Psilocybin induced change of cardiac electrophysiology

- **Blood pressure**
  - Increased blood pressure is apparent at 60-90min

- **Temperature**
  - No significant changes
Physiological Effects

- **Neuroendocrine data**
  - TSH, prolactin, ACTH, and cortisol levels were increased at t+105min, returned back to baseline at t+300min

- **Blood chemistry**
  - At high doses, liver function tests (GGT and AST) were elevated at t+105 min and returned to normal at t+300
Psychological Effects

- Serotonin receptors (5-HT) play an important role in perception, affect regulation, and attention.
- Doses between 45-315 mcg/kg are clearly rated as psychoactive.
  - Dose dependent changes in mood, sensory perception, as well as time, space, and self perception.
  - Effects last about 3 to 6 hours.

Addict Biol. 2002;7(4):357-64.
Literature Review
Symptom Scales

- **Beck Depression Inventory (BDI)**
  - Series of questions developed to measure the intensity, severity, and depth of depression

- **Hospital Anxiety and Depression Scale (HADS)**
  - Commonly used by doctors to determine levels of anxiety and depression that a patient is experiencing

- **State-Trait Anxiety Inventory (STAI)**
  - Self-reported assessment of anxiety, differentiates between the temporary condition of state anxiety and the more general and long-standing quality of trait anxiety

- **Hamilton Anxiety/Depression Rating Scale (HAM-A, HAM-D)**
  - Clinician rated scales to assess severity of anxiety/depression

- Profile of Mood States
- Brief Psychiatric Rating Scale
- 5-Dimension Altered States of Consciousness Profile
Pilot Study of Psilocybin Treatment for Anxiety in Patients with Advanced Stage Cancer


Objective

• To explore the safety and efficacy of psilocybin in patients with advanced-stage cancer and reactive anxiety

Design

• Double-blind, placebo-controlled study
• Crossover design

Intervention

• Psilocybin 0.2 mg/kg
• Placebo (niacin 250mg)
Inclusion
- Advanced stage-cancer
- DSM-IV diagnosis of acute stress disorder due to cancer or adjustment disorder with anxiety

Exclusion
- Central nervous system involvement of the cancer
- Severe CV illness
- Abnormal hepatic and renal function
- Diabetes
- Lifetime history of schizophrenia, bipolar disease, other psychiatric illness
- Anxiety of affective disorder within 1 year prior to cancer diagnosis
- Contraindicated medications

Endpoints
- **Primary:**
  - Safety and subject experience
  - Beck Depression Inventory (BDI)
  - Profile of Mood States (POMS)
  - State-Trait Anxiety Inventory (STAI)
- **Additional:**
  - 5-Dimension Altered States of Consciousness profile (5D-ASC)
  - Brief Psychiatric Rating Scale

12 subjects
(11 women, 36 to 58 years old)

- 4 breast cancer
- 3 colon cancer
- 2 ovarian cancer
- 1 salivary gland cancer
- 1 peritoneal cancer
- 1 multiple myeloma

- 12 participants
- 11 participants
- 8 participants

BDI, POMS, STAI

Day -1

POMS, STAI, 5D-ASC, Brief Psychiatric Rating Scale

Day 0

BDI, POMS, STAI

Day +1

BDI, POMS, STAI

Day +14

BDI, POMS, STAI

Monthly

BDI – Beck Depression Inventory
POMS – Profile of Mood States
STAI – State- Trait Anxiety Inventory
5D-ASC – 5-Dimension Altered State Of Consciousness Profile

5-Dimension Altered State of Consciousness Profile

Oceanic Boundlessness

Visionary Restructuralization

Anxious Ego Dissolution
Summary
- Safe physiologically and psychologically
- Profile of Mood States
  - Improvement during 2 weeks post treatment
- Beck Depression Inventory
  - Significant improvement at 6mo
- State- Trait Anxiety Inventory
  - Downward trend in trait anxiety

Limitations
- Small sample size
- Not generalizable population
- Treatment order apparent to participants
Rapid and Sustained Symptom Reduction Following Psilocybin Treatment for Anxiety and Depression in Patients with Life-Threatening Cancer: A Randomized Controlled Trial

To determine if psilocybin in conjunction with targeted psychotherapy would significantly decrease anxiety and depression symptoms in patients with life-threatening cancer diagnosis.

**Objective**

- Double-blind, randomized, controlled study
- Crossover design

**Intervention**

- Psilocybin 0.3 mg/kg
- Placebo (Niacin 250 mg)

**Inclusion**
- 18 to 76 years old
- Projected life expectancy of at least 1 year
- Terminal cancer diagnosis
- Primary diagnosis of Acute Stress Disorder, GAD, Anxiety Disorder due to cancer, Adjustment Disorder with Anxiety +/- Depression

**Exclusion**
- HADS <8
- Epilepsy, renal disease, diabetes, abnormal liver function, severe CV disease
- Personal or immediate family history of schizophrenia, bipolar disorder, delusional disorder, paranoid disorder, or schizoaffective disorder
- Current substance use disorder

**Endpoints**
- **Primary:**
  - Hospital Anxiety and Depression Scale (HADS)
  - Beck Depression Inventory (BDI)
  - State-Trait Anxiety Inventory (STAI)
- **Additional:**
  - Cardiovascular measures (HR, BP)
  - Adverse events

31 subjects
(90% Caucasian, 62% women)

31% breast cancer
28% reproductive cancer
17% GI cancer
14% hematologic cancer
10% other

Dose 1
29 subjects
6 wk
28 subjects
Dose 2
26 subjects
6 wk
24 subjects
6 mo
23 subjects


Summary

- Robust, rapid, and long-lasting anxiolytic and antidepressant effects in patients
  - At 7 weeks sustained reduction in BDI, HADS, STAI

Limitations

- Crossover design
- Psilocybin or psychotherapy
- Sample size, lack of generalizability
Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patient with Life-Threatening Cancer: A Randomized Double-Blind Trial

To determine the efficacy of a classic hallucinogen for treatment of depressed mood and anxiety in psychologically distressed cancer patients.

- Double-blind, randomized, controlled study
- Crossover design

- Psilocybin high dose (22 or 30mg/70kg)
- Psilocybin low dose (1 or 3mg/70kg)
Inclusion

- 21 to 80 years old
- Life-threatening cancer diagnosis
- DSM-IV diagnosis that included: GAD, Acute Stress Disorder, PTSD, MDD, Dysthymic Disorder, Adjustment Disorder with anxiety

Exclusion

- Cancer with known CNS involvement
- Hepatic dysfunction
- CV conditions (HTN, angina Afib, TIA, stroke)
- Epilepsy, Renal insufficiency, Insulin-dependent diabetes
- Current psychoactive medications
- Potent metabolic inducers or inhibitors
- Psychiatric exclusions

Endpoints

- Primary:
  - Hamilton Depression/Anxiety Rating Scale (HAM-D and -A)
  - Hospital Anxiety and Depression Scale (HADS)
  - Beck Depression Inventory (BDI)
  - State-Trait Anxiety Inventory (STAI)
- Additional:
  - Cardiovascular measures
  - Adverse effects

51 subjects
(94% Caucasian, 49 % women)

13 breast cancer
7 aerodigestive cancer
4 GI cancer
18 genitourinary cancer
8 hematologic malignancies
1 other cancer

Dose 1
51 subjects

Dose 2
49 subjects

6 mo
46 subjects


Baseline

- Anxiety Depression
- BP/HR, AE

Dose 1

- Anxiety Depression
- 5 weeks
- BP/HR, AE

Dose 2

- Anxiety Depression
- 5 weeks
- BP/HR, AE

6 months

- Anxiety Depression

Star symbol indicates a significant difference between the two groups at the Post-session 1 time-point ($p<0.05$, planned comparison). Cross symbol indicates a significant difference between the Post-session 1 and Post-session 2 time-points in the Low-Dose-1st (High-Dose-2nd) Group ($p<0.05$, planned comparison).

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<table>
<thead>
<tr>
<th>Measure</th>
<th>Group</th>
<th>Assessment time-point</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Baseline(^a)</td>
<td>Post-session (^b)</td>
<td>Post-session (^c)</td>
<td>6 months(^d)</td>
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<tr>
<td>HADS Total</td>
<td>Low-Dose-1st (High-Dose-2nd)</td>
<td>20.52 (0.92)</td>
<td>12.04 (1.18)</td>
<td>9.17 (1.15)*</td>
<td>9.32 (1.22)</td>
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<td>High-Dose-1st (Low-Dose-2nd)</td>
<td>20.88 (0.89)</td>
<td>9.31 (1.29)</td>
<td>8.96 (1.53)</td>
<td>8.17 (1.16)</td>
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<td>HADS Anxiety</td>
<td>Low-Dose-1st (High-Dose-2nd)</td>
<td>11.04 (0.60)</td>
<td>6.00 (0.59)</td>
<td>4.91 (0.60)</td>
<td>4.68 (0.67)</td>
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<td>High-Dose-1st (Low-Dose-2nd)</td>
<td>11.08 (0.53)</td>
<td>5.38 (0.78)</td>
<td>4.68 (0.75)</td>
<td>4.71 (0.65)</td>
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<td>STAI State Anxiety</td>
<td>Low-Dose-1st (High-Dose-2nd)</td>
<td>42.00 (1.76)</td>
<td>37.48 (2.49)</td>
<td>32.83 (2.21)*</td>
<td>32.73 (2.38)</td>
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<td>High-Dose-1st (Low-Dose-2nd)</td>
<td>45.77 (1.98)</td>
<td>34.36 (2.17)</td>
<td>31.56 (2.02)</td>
<td>30.25 (1.98)</td>
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<tr>
<td>Death Transcendence Scale</td>
<td>Low-Dose-1st (High-Dose-2nd)</td>
<td>122.12 (4.39)</td>
<td>127.66 (3.92)</td>
<td>136.00 (3.62)**</td>
<td>133.36 (3.91)</td>
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<tr>
<td></td>
<td>High-Dose-1st (Low-Dose-2nd)</td>
<td>117.85 (3.34)</td>
<td>128.46 (3.99)</td>
<td>127.25 (4.09)</td>
<td>128.96 (4.07)</td>
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<td>Purpose in Life</td>
<td>Low-Dose-1st (High-Dose-2nd)</td>
<td>96.16 (3.32)</td>
<td>101.80 (3.78)</td>
<td>106.92 (3.63)*</td>
<td>108.00 (3.36)</td>
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<td>High-Dose-1st (Low-Dose-2nd)</td>
<td>91.04 (3.43)</td>
<td>106.19 (3.04)</td>
<td>107.00 (3.73)</td>
<td>108.08 (3.71)</td>
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<tr>
<td>LAP-R Coherence</td>
<td>Low-Dose-1st (High-Dose-2nd)</td>
<td>35.25 (2.36)</td>
<td>38.14 (2.52)</td>
<td>43.00 (2.31)*</td>
<td>43.25 (2.09)</td>
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<td>High-Dose-1st (Low-Dose-2nd)</td>
<td>30.86 (1.91)</td>
<td>36.83 (2.01)</td>
<td>39.30 (2.05)</td>
<td>40.25 (1.93)</td>
</tr>
</tbody>
</table>

\(^a\)Baseline, \(^b\)Post-session 1, \(^c\)Post-session 2, \(^d\)6 months

\(^*p<0.05, \)**p<0.01, \(**p<0.001\)

Summary

- Long term clinical response to treatment (83%) at 6 months
- Patients expected psilocybin both times, less expectancy effects
- Higher incidence of adverse effects

Limitations

- Not diverse population
  - >90% Caucasian, college or post-graduate education
- Crossover design
Summary and Conclusion
## Summary

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<tr>
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<tbody>
<tr>
<td>Dosing</td>
<td>Psilocybin 0.2 mg/kg Niacin 250 mg</td>
<td>Psilocybin 0.3 mg/kg Niacin 250 mg</td>
<td>Psilocybin 0.3 or 0.4mg/kg Niacin 250 mg</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Psilocybin 0.01 or 0.04mg/kg</td>
</tr>
<tr>
<td>Participants</td>
<td>12 cancer patients</td>
<td>31 cancer patients</td>
<td>51 cancer patients</td>
</tr>
<tr>
<td>Follow-up</td>
<td>6 month follow-up</td>
<td>6 month follow-up</td>
<td>6 month follow-up</td>
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<tr>
<td>Monitoring</td>
<td>Brief contact to check-in during session</td>
<td>Professional psychotherapy pre and post session</td>
<td>Session monitors, introduced pre session</td>
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<tr>
<td>Outcome</td>
<td>STAI – trend</td>
<td>7 weeks sustained reduction in BDI, HADS, STAI</td>
<td>6 month clinical significant response (83% HAM-A)</td>
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</tbody>
</table>
Psilocybin is safe to use in a very narrow patient population with end of life anxiety

- End organ damage
- Serotonergic drugs
- Chronic diseases

Not enough safety and efficacy data to use as standard of care

Inconsistent study design creates biased results
Patient Case

“I am so anxious that it is hard to think about anything else. I had lost my faith because of anxiety and it is terrifying.”

AL is a 53 year old woman with a diagnosis of metastatic ovarian cancer. Patient is currently receiving palliative treatment for pain and nausea. She has been suffering from anxiety and depression since her diagnosis 3 months ago.

Is this patient a good candidate for Psilocybin therapy?

“Annie’s mood remained greatly improved for some time after the treatment. She also had much less anxiety, and her fear of getting sicker and her fear of the dying process also diminished a great deal. Beyond that, she and I got along much better after her psilocybin treatment … I have no doubt that the treatment Annie went through was of great value to her …”
Future Direction

- Promising results warrant a need for further investigation
  - Larger, more diverse population
  - Study design
- Exploring other hallucinogenic drugs and their potential medical use
  - MDMA for PTSD
  - Psilocybin for treatment-resistant depression and anxiety
- Granting access to Schedule I drugs for research and medical use
Acknowledgment

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- Stephen Saklad, PharmD, BCPP
- Katerine Getchell, PharmD, BCACP
- CTVHCS Co-Residents and Preceptors
# References


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