Psilocybin-Assisted Psychotherapy for Psychiatric Illness: Research Update

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Faculty Disclosure

- **Dr. Woolley**: Employee—University of California, San Francisco (UCSF), San Francisco VA Medical Center (SFVA); Site Principal Investigator (UCSF)—psilocybin Phase 2 trial (sponsored by Usona Institute), MDMA Phase 3 trial (sponsored by MAPS); Research Support (UCSF)—Heftter Research Institute, Usona Institute.
Disclosure

• The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
  – Psilocybin does not have an FDA-approved indication for any psychiatric disorder.

• Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

• This activity has been independently reviewed for balance.
Learning Objectives

• Assess the psychotherapeutic benefits and risks of psilocybin-assisted psychotherapy

• Compare and contrast psilocybin-assisted psychotherapy with current models of mental health treatment involving psychiatric medications +/- psychotherapy

• Discuss the current status of the field of psilocybin-assisted psychotherapy, including its current legal and regulatory status
Psilocybin

• Active ingredient in over 180 species of hallucinogenic mushroom

• Used in religious and healing practices in various cultures for centuries

• Predominant 5-HT$_{2A}$ receptor agonist

• 5 to 6 hours duration

• Potent effects on mood, cognition, and behavior
  – “Like dreaming while awake”


Psilocybin

**Timeline**

**1959**: Isolated from *P. Mexicana*

**1950–1960s**: Produced by Sandoz

**1971**: CSA Schedule I substance

**1990s**: Human study at UNM (not published)

**2004**: FDA-approved clinical trial for anxiety in late-stage cancer

**Pharmacodynamics**

Rapidly dephosphorylated to psilocin

Mixed serotonin agonist

Primary effects through 5-HT$_{2A}$ receptor

**Pharmacokinetics**

Dose 14–30.1 mg/70 kg PO

Metabolism

– UDP-glucuronosyltransferases

– < 2% renally excreted unchanged

CSA = Controlled Substance Act; UNM = University of New Mexico.

Psilocybin

Clinical Experience and Safety

1950–1960s
Participants: > 350 in > 13 studies

1960–1980s
Patients: > 1500 in various clinical contexts

2000–2019
Participants: > 275 (patients + healthy volunteers)
Serious Adverse Events: Zero

US Food and Drug Administration Investigational New Drug (IND) 113080.
Psilocybin (not Psilocybe mushrooms) is used in modern clinical trials vs caffeine.
Psilocybin \rightarrow Psilocin
Psilocin is an agonist at Serotonin 1A, 2A, 2C Receptors
Psilocybin Can Occasion Mystical-Type Experiences Having Substantial and Sustained Personal Meaning and Spiritual Significance

- 2 to 3, 8-hour sessions at 2-month intervals
  - Psilocybin (30 mg/70 kg) or methylphenidate (40 mg/70 kg) administered at beginning of session

- Follow-up surveys administered 2 months after each session

- Double-blind, crossover design

- N=24 (average age = 46 years, 58% male, healthy)

Psilocybin Raises Blood Pressure

Monitor Ratings during Sessions

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Description</th>
<th>MPH</th>
<th>Psilocybin</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Persisting Effects Questionnaire</strong></td>
<td><strong>Description</strong></td>
<td><strong>MPH</strong></td>
<td><strong>Psilocybin</strong></td>
<td><strong>P value</strong></td>
</tr>
<tr>
<td></td>
<td>Positive attitudes about life and/or self</td>
<td>22.8 (4.5)</td>
<td>55.0 (5.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Negative attitudes about life and/or self</td>
<td>0.3 (0.1)</td>
<td>0.5 (0.3)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Positive mood changes</td>
<td>16.0 (3.5)</td>
<td>39.2 (5.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Negative mood changes</td>
<td>0.6 (0.5)</td>
<td>1.5 (0.7)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Altruistic/positive social effects</td>
<td>17.3 (4.4)</td>
<td>46.6 (5.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Antisocial/negative social effects</td>
<td>0.3 (0.2)</td>
<td>0.7 (0.5)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Positive behavior changes</td>
<td>29.2 (6.5)</td>
<td>60.0 (4.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Negative behavior changes</td>
<td>1.7 (1.2)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Did the experience change your sense of well-being or life satisfaction?</td>
<td>+0.79 (0.18)</td>
<td>+2.04 (0.17)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Community Observer Ratings</strong></td>
<td>Positive change score</td>
<td>-0.03 (0.68)</td>
<td>2.42 (0.70)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>
Psilocybin Experiences are Very Personally Meaningful

Psilocybin Binds to $5\text{-HT}_{2\text{A}}$ Receptors across the Cortex

Psychedelic Effects of Psilocybin Correlate with Plasma Psilocin Levels

And 5-HT$_{2A}$ Receptor Occupancy

Psilocybin Decreases Global Brain Perfusion

But Increases Relative Brain Perfusion

Summary

gCBF = global cerebral blood flow; IFG = inferior frontal gyrus; rCBF = regional cerebral blood flow.
Psilocybin Decreases Amygdala Reactivity

And Increases Positive Affect

PANAS = Positive and Negative Affect Schedule; STAI = State-Trait Anxiety Inventory.
And the Two are Correlated

Psychedelic-Assisted Psychotherapy

(No Rx) Preparation sessions  
(~ 6–8 hours)

(Rx) Treatment session  
(~ 8 hours)

(No Rx) Integration sessions  
(~ 4–8 hours)
Important Elements of Psychedelic-Assisted Psychotherapy

• **Preparation** – create sense of safety and holding environment

• **Nondirective** approach to therapy

• **Beginner’s Mind** – setting aside expectations

• Trust in an **Inner Healing Capacity**

• **Music**

• **Integration** – essential and ongoing
21st Century Human Research with Psilocybin

Clinical Indications
- Existential Distress and Depression
- Obsessive-Compulsive Disorder
- Tobacco Use Disorder
- Alcohol Use Disorder
- Cocaine Use Disorder

Clinical and Non-clinical Studies
- Total participants ~ 600
- > 2000 doses administered
- Zero Significant Adverse Events
Psilocybin and FDA Drug Development

OCD = obsessive-compulsive disorder.
Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients with Life-Threatening Cancer

5-week crossover of psilocybin:
Low dose (1 mg/70 kg or 3 mg/70 kg) vs High dose (22 mg/70 kg or 30 mg/70 kg)

N=51 (49% women) with potentially life-threatening cancer diagnosis and DSM diagnosis:
- Adjustment disorder, chronic
- Dysthymia (mild depression)
- GAD
- MDD

GAD = generalized anxiety disorder; MDD = major depressive disorder.
Safety Outcomes

Significant Adverse Events
 Zero

Adverse Events
 Hypertension
 Nausea / vomiting
 Anxiety
 Paranoia
 Headaches

HAMD = Hamilton Rating Scale for Depression.
HADS = Hospital Anxiety and Depression Scale; HAM-A = Hamilton Anxiety Rating Scale; LAP-R = Life Attitude Profile-Revised; POMS = Profile of Mood States.

## Meaningfulness and Spiritual Significance

<table>
<thead>
<tr>
<th>Questionnaire and subscale description</th>
<th>Assessment time-point</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low dose (5 weeks)</td>
<td>High dose (5 weeks)</td>
</tr>
<tr>
<td>How personally meaningful was the experience? (maximum score=8)</td>
<td>4.62 (0.31)</td>
<td>6.38 (0.20)***</td>
</tr>
<tr>
<td>Top 5 most meaningful of life, including single most (% of participants)</td>
<td>24%</td>
<td>62%***</td>
</tr>
<tr>
<td>How spiritually significant was the experience? (maximum score=6)</td>
<td>3.16 (0.24)</td>
<td>4.46 (0.19)***</td>
</tr>
<tr>
<td>Top 5 most spiritually significant of life, including single most (% of participants)</td>
<td>24%</td>
<td>66%***</td>
</tr>
</tbody>
</table>

Rapid and Sustained Symptom Reduction following Psilocybin Treatment for Anxiety and Depression in Patients with Life-Threatening Cancer

- 2 sessions of psychotherapy over 9 months
  - Psilocybin (21 mg/70 kg) or niacin (250 mg) at the beginning of the session

- Follow-up assessment performed 26 weeks after second session

- Double-blind, randomized, crossover design

- N=14 (average age = 56 years, 38% male, cancer comorbid with depression or anxiety)

BDI = Beck Depression Inventory.
<table>
<thead>
<tr>
<th>General themes</th>
<th>Case occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relational Embeddedness</td>
<td>13</td>
</tr>
<tr>
<td>Emotional Range</td>
<td>13</td>
</tr>
<tr>
<td>Role of Music as Conveyor of Experience</td>
<td>13</td>
</tr>
<tr>
<td>Meaningful Visual Phenomena</td>
<td>13</td>
</tr>
<tr>
<td>Wisdom Lessons</td>
<td>13</td>
</tr>
<tr>
<td>Revised Life Priorities</td>
<td>13</td>
</tr>
<tr>
<td>Desire to Repeat the Psilocybin Experience</td>
<td>12</td>
</tr>
<tr>
<td>Typical themes</td>
<td></td>
</tr>
<tr>
<td>Exalted Feeling of Joy or Bliss</td>
<td>11</td>
</tr>
<tr>
<td>Feeling Love</td>
<td>11</td>
</tr>
<tr>
<td>Ineffability</td>
<td>10</td>
</tr>
<tr>
<td>Alterations to Identity During Psilocybin Experience</td>
<td>9</td>
</tr>
<tr>
<td>Embodiment</td>
<td>7</td>
</tr>
<tr>
<td>From Separateness to Interconnectedness</td>
<td>7</td>
</tr>
<tr>
<td>Difficult Struggle: Experiences of Transient</td>
<td>7</td>
</tr>
<tr>
<td>Psychological Distress</td>
<td>7</td>
</tr>
<tr>
<td>Loved Ones as Guiding Spirits</td>
<td>7</td>
</tr>
<tr>
<td>Sharing the Experience With Loved Ones</td>
<td>7</td>
</tr>
</tbody>
</table>

Psilocybin Trial Participants
"It led to a re-awakening of what it felt like when my first daughter, Tanya, died. And the feelings just came flooding up. I was completely into the sense of despair and loss that I had when she died. And I howled. And I felt comforted that my guides won’t come and comfort they won’t stop me, they’ll let me go into it. And I did. And that was almost 30 years of, not denial, but putting it down, suppressing of what that felt. And that was very liberating."
Treatment-Resistant Depression

N=12.
QIDS = Quick Inventory of Depressive Symptoms.
Smoking Cessation

• 2 to 3 psilocybin doses (20–30 mg/70 kg) given on weeks 5, 7, and 13 of 15-week treatment program

• Follow-ups at 10 weeks, 6 months, and 12 months
  – Urine and breath samples collected at week 10

• N=15 (average age = 51 years, 67% men, nicotine dependence with previous attempt[s] to quit)

Alcohol Dependence

- Psilocybin (14 mg/70 kg) administered during 2 sessions 4 weeks apart
- Single-group design
- Data collected over 36 weeks
- N=10 (average age = 40 years, 60% men, DSM-IV alcohol dependence)

# Summary of Clinical Studies on Psilocybin for Substance Use Disorders

<table>
<thead>
<tr>
<th>Status</th>
<th>Authors/Institution</th>
<th>Outcomes</th>
<th>Study Design</th>
<th>N</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed, published 2014</td>
<td>Johnson, et al. John Hopkins</td>
<td>Safety Tobacco smoking abstinence</td>
<td>Open label pilot study 2–3 drug treatment sessions</td>
<td>15</td>
<td>80% demonstrated biological abstinence at 6-month follow-up</td>
</tr>
<tr>
<td>Ongoing</td>
<td>John Hopkins</td>
<td>Tobacco smoking abstinence</td>
<td>RCT; 1 drug treatment session with psilocybin or nicotine replacement therapy patch</td>
<td>95</td>
<td>N/A</td>
</tr>
<tr>
<td>Completed, published 2015</td>
<td>Bogenschutz, et al. UNM</td>
<td>Safety Alcohol cravings Heavy drinking days</td>
<td>Open-label pilot study 2 drug treatment sessions</td>
<td>10</td>
<td>Increase in abstinence from alcohol $P&lt;.05$ and reduced cravings $P&lt;.001$ at 36 weeks No serious adverse events</td>
</tr>
<tr>
<td>Ongoing</td>
<td>NYU and UNM</td>
<td>Safety Heavy drinking days</td>
<td>Randomized double-blind trial 1–2 drug treatment sessions with psilocybin or diphenhydramine</td>
<td>180</td>
<td>N/A</td>
</tr>
<tr>
<td>Ongoing</td>
<td>University of Alabama at Birmingham</td>
<td>Cocaine abstinence</td>
<td>Randomized double-blind trial 1 drug treatment session with psilocybin or diphenhydramine</td>
<td>40</td>
<td>N/A</td>
</tr>
<tr>
<td>Coming soon…</td>
<td>University of Wisconsin at Madison</td>
<td>Methamphetamine use reduction</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Psilocybin at UCSF: Long-Term AIDS Survivors

Brian Anderson, MD
Long-Term AIDS Survivors

Diagnosed early in the AIDS Epidemic

Formerly “terminally ill”

2015: > 50% HIV+ in the United States are > 50 years old
Long-Term AIDS Survivors

- Chronic Existential Distress
- Traumatic Loss / Complicated Grief
- Isolation and Loneliness
- Depression
- Risky Substance Use and Sex
- Anecdotally: High Suicide Rate

Photo: San Francisco Chronicle.
Study Design

Design
Psilocybin-assisted group psychotherapy
Phase 1, single-arm, open-label
N=18 (3 groups of 6)

Primary Outcomes
1. Safety
2. Feasibility
3. Primary: Demoralization (Baseline – Endpoint)
4. Secondary: PTSD symptoms (Baseline – Endpoint)

PTSD = posttraumatic stress disorder.
Study Design

Inclusion
LTAS
Gay-identified men > 50 years old
Moderate-to-severe Demoralization (DS-II)

Exclusion
Antidepressants, mood stabilizers, antipsychotics
Psychiatric instability
Unstable cardiovascular or other major medical disease
Abnormal ECG and basic laboratory studies

DS-II = Demoralization Scale-II; ECG = electrocardiogram; LTAS = long-term AIDS survivors.
Study Design

Brief Supportive-Expressive Group Therapy

90-minute sessions; 2 group therapists

Process group; “here and now” oriented

Mutual support, expression of emotion, active coping skills

## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59.2 (4.4)</td>
<td>49.5–66</td>
</tr>
<tr>
<td>Montreal Cognitive Assessment (MoCA)</td>
<td>27.9 (1.4)</td>
<td>24–30</td>
</tr>
<tr>
<td>Lifetime: People close to you who have died</td>
<td>25.8 (26.9)</td>
<td>2–100</td>
</tr>
<tr>
<td>Lifetime: Psychedelic use</td>
<td>29.8 (52.3)</td>
<td>0–200</td>
</tr>
<tr>
<td>Years since last used psychedelics</td>
<td>15.8 (19)</td>
<td>1 mo–46 yrs</td>
</tr>
</tbody>
</table>
Screening, Enrollment, and Retention:
Nov 2017 – Jan 2019

91 participants assessed via phone screen

37 eligible for Enrollment Evaluation

30 consented and completed evaluation

18 initiated treatment and administered psilocybin

17 completed treatment

18 completed primary endpoint assessment

18 completed safety assessment at 3-Month Follow-up

54 ineligible for evaluation

7 declined evaluation

11 ineligible, 1 declined

1 discontinued treatment (adverse event)

Group therapy attendance = 95%
## Current SCID-5 Diagnoses at Enrollment

**Evaluated for:** MDD, GAD, Panic Disorder, OCD, Cluster B Personality Disorders

<table>
<thead>
<tr>
<th>Participant</th>
<th>Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>GAD, PCL-5 = 35</td>
</tr>
<tr>
<td>#2</td>
<td>MDD, GAD, Panic, PCL-5 = 51</td>
</tr>
<tr>
<td>#3</td>
<td>MDD</td>
</tr>
<tr>
<td>#4</td>
<td>MDD</td>
</tr>
<tr>
<td>#5</td>
<td>MDD, GAD, Panic, BPD</td>
</tr>
<tr>
<td>#6</td>
<td>GAD, Panic, BPD</td>
</tr>
<tr>
<td>#7</td>
<td>MDD, GAD, BPD, PCL-5 = 49</td>
</tr>
<tr>
<td>#8</td>
<td>GAD</td>
</tr>
<tr>
<td>#10–18</td>
<td>None</td>
</tr>
</tbody>
</table>

BPD = borderline personality disorder; PTSD Checklist for DSM-5 = PCL-5; SCID-5 = Structured Clinical Interview for DSM-5.
## Serious Adverse Events

<table>
<thead>
<tr>
<th>SAE Primary Term</th>
<th># of Participants (%)</th>
<th>Relatedness to Psilocybin</th>
<th>Highest Severity Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>During Trial</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Cell Carcinoma Recurrence, Metastatic</td>
<td>1 (6%)</td>
<td>Unrelated</td>
<td>Severe</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>1 (6%)</td>
<td>Unrelated</td>
<td>Severe</td>
</tr>
<tr>
<td><strong>During Follow-up</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimulant-induced Psychosis</td>
<td>1 (6%)</td>
<td>Unrelated</td>
<td>Potentially life-threatening</td>
</tr>
<tr>
<td>Suicide Attempt</td>
<td>1 (6%)</td>
<td>Unrelated</td>
<td>Potentially life-threatening</td>
</tr>
</tbody>
</table>

### Suicidality

**C-SSRS**: No clinically significant change from Baseline to Endpoint
<table>
<thead>
<tr>
<th>AE Primary Term</th>
<th># of Participants (%)</th>
<th>Highest Severity Observed</th>
<th>Expectedness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 (33%)</td>
<td>Severe</td>
<td>Expected</td>
</tr>
<tr>
<td>Paranoia / ideas of reference</td>
<td>4 (22%)</td>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>Thought disorder</td>
<td>1 (6%)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td><strong>Non-psychiatric</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (94%)</td>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Tachycardia</td>
<td>2 (11%)</td>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (33%)</td>
<td>Mild</td>
<td></td>
</tr>
<tr>
<td>Motor agitation / marked restlessness</td>
<td>4 (22%)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Unsteady gait / ataxia</td>
<td>4 (22%)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>3 (17%)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Physical discomfort / pain</td>
<td>1 (6%)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>1 (6%)</td>
<td>Moderate</td>
<td>Expected</td>
</tr>
</tbody>
</table>
### Post-Medication Visit Adverse Events

**Psilocybin-Related**

<table>
<thead>
<tr>
<th>AE Primary Term</th>
<th># of Participants (%)&lt;br&gt;( n=18 )</th>
<th>Highest Severity Observed</th>
<th>Expectedness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>8 (44%)</td>
<td>Mild</td>
<td>Expected</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (11%)</td>
<td>Moderate</td>
<td>Expected</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2 (11%)</td>
<td>Mild</td>
<td>Expected</td>
</tr>
<tr>
<td>Anxiety Exacerbation</td>
<td>1 (6%)</td>
<td>Severe Moderate</td>
<td>Expected</td>
</tr>
<tr>
<td>Methamphetamine relapse</td>
<td></td>
<td></td>
<td>Unexpected</td>
</tr>
<tr>
<td>Post-traumatic Stress</td>
<td>1 (6%)</td>
<td>Moderate</td>
<td>Unexpected</td>
</tr>
<tr>
<td>Flashback</td>
<td></td>
<td></td>
<td>Expected</td>
</tr>
<tr>
<td>Tinnitus</td>
<td></td>
<td></td>
<td>Expected</td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td>Expected</td>
</tr>
<tr>
<td>Panic</td>
<td></td>
<td></td>
<td>Expected</td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
<td>Expected</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (6%)</td>
<td>Mild</td>
<td>Expected</td>
</tr>
</tbody>
</table>
PTSD Checklist 5
(Mean, N=18)

Baseline Preparation Week 1-2 Endpoint
(Week 3-4)
3 Month Follow Up

PTSD Likely

Psilocybin
*P=.004, Hedge’s g=.74

PTSD Unlikely

4 Group Therapy Sessions

4–6 Group Therapy Sessions
Challenging Experiences

ChEQ

Looking back on the entirety of your session, please rate the degree to which at any time during that session you experienced the following phenomena. Circle the corresponding number according to your feelings, thoughts, and experiences at the time of the session. In making each of your ratings, use the following scale:

0 - None; not at all
1 - So slight cannot decide
2 - Slight
3 - Moderate
4 - Strong
5 - Extreme (more than ever before in my life)

<table>
<thead>
<tr>
<th>Factor</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Isolation and loneliness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>2. Sadness</td>
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<td>3. Feeling my heart beating</td>
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<td>4. I had the feeling something horrible would happen</td>
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<td>5. Feeling my body shake/tremble</td>
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<td>6. Feelings of grief</td>
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<td>7. Experience of fear</td>
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<td>8. Fear that I might lose my mind or go insane</td>
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Discussion

Psilocybin-assisted group therapy is feasible

Psilocybin therapy in demoralized LTAS can be safe

Large effect sizes on pre-post demoralization, PTSD symptoms
Limitations

Open-label, no control arm

Poor generalizability (LTAS)

Non-standard clinical indication

Selection bias, expectancy effects
Summary

• Psilocybin is safe to administer in controlled medical settings

• Psilocybin-assisted therapy shows promising effects for demoralization, depression, and substance use disorders although studies are small and not well controlled

• Binds to 5-HT$_{2A}$ receptors which appear to mediate psychological effects

• Causes widespread neural changes including altering resting state networks and amygdala processing
  – However, clinical mechanisms of action are unclear