Psilocybin at the End of Life

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DISCLOSURE OF FINANCIAL RELATIONSHIPS

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• None of my slides and/or handouts contain any advertising, trade names or product-group messages. Any treatment recommendations I make will be based on clinical evidence or guidelines.
Overview

- Ethnobotany
- Anthropology
- Chemistry and toxicity
- Clinical research
- Using hallucinogens with cancer patients
- Current research
- Methodology & approval process
- Study Results
The Ethnobotany of Psilocybin
- 186 known psilocybin species
- Increasing distribution
Found in most parts of the world

- Affection for “disturbed areas”
- Follow human expansion
- Found where people congregate

Co-evolved with humans
(Domestication of cattle)
The Anthropology of Psilocybin

Gold Pectorals from the Sinú culture of Colombia
(1200 - 1600 c.e.)
The Anthropology of Psilocybin

- Mesoamerican healers

“The course of human history has been dramatically affected by the use of psilocybin mushrooms and will continue to be for years to come.”

— Paul Stamets
The Anthropology of Psilocybin

“And when the effects of the mushrooms had left them, they consulted among themselves and told one another what they had seen in vision.”

From *The Florentine Codex* by Bernardino de Sahagún (circa 1600)
Repression of Plant Hallucinogens

The Holy Inquisition of Mexico (1616)
Proclamation condemning the use of plant hallucinogens in the new world
Then in 1629, Hernando Ruiz de Alarcon (a Spanish Inquisitor), wrote of the idolatries he had observed when the native Indians consumed their ritual hallucinogens: "which when drunk deprive of the senses, because it is very powerful, and by this means they communicate with the devil, because he talks to them when they are deprived of judgment with the said drink, and deceive them with different hallucinations, and they attribute it to a god they say is inside the seed . . ."
The Anthropology of Psilocybin

Sacramental use for 7,000+ years

- Religious and medicinal uses
- Used by widely diverse cultures
- Influenced religion, philosophy, art
The Anthropology of Psilocybin

Seeking The Magic Mushroom
by
R. Gordon Wasson

“A New York banker goes to Mexico’s mountains to participate in the age-old rituals of Indians who chew strange growths that produce visions.”
The Anthropology of Psilocybin

A New York Banker and a Mexican Shaman bring psilocybin into the modern age.

R. Gordon Wasson

Maria Sabina gives Wasson a mushroom
"Geometric patterns, angular not circular, in richest colors, such as might adorn textiles or carpets. Then the patterns grew into architectural structures, with colonnades and architraves, patios of regal splendor, the stone-work all in brilliant colors, gold and onyx and ebony, all most harmoniously and ingeniously contrived, in richest magnificence extending beyond the reach of sight, in vistas measureless to man . . . They seemed to belong . . . to the imaginary architecture described by the visionaries of the Bible".

- Wasson in *Life* Magazine, 1957
“Mental effects of mushroom poisoning” by the mycologist Worthington Smith, published in *The Graphic*, 15 November 1873.
The Chemistry of Psilocybin

Serotonin

Psilocybin
Psilocin
The Chemistry of Psilocybin

- $C_{12}H_{17}N_2O_4P$
- Tryptamine family of indoles
- Close resemblance to serotonin
- Low toxicity
The Chemistry of Psilocybin

- 4-phosphoryloxy-N,N-dimethyltryptamine
- Substituted indolealkylamine/hallucinogenic tryptamine
- 5-HT 2A and 5-HT 2C receptor agonists
- Medium dose psilocybin (12-20 mg.) produces a well-controlled altered state of consciousness.
- Effects last from 4 to 6 hours
The Chemistry of Psilocybin

Figure 3. Course of clinical effects of LSD, psilocybin and CZ-74 (a psilocybin-derivative).\(^{13}\)
The Chemistry of Psilocybin

Figure 4. Time-course of plasma levels for psilocin after 0.224 mg/kg body weight psilocybin p.o. (n = 6).
Figure 5. Mean urine excretion rate of psilocin after 0.224 mg/kg psilocybin p.o. (n = 8).
The Chemistry of Psilocybin

### The psilocometric scale of comparative potency of selected *Psilocybe* mushrooms

<table>
<thead>
<tr>
<th>SPECIES</th>
<th>% PSilocybin</th>
<th>% Psilocin</th>
<th>% Baeocystin</th>
<th>REFERENCE</th>
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<tr>
<td><em>P. azurescens</em></td>
<td>1.78</td>
<td>.38</td>
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<td><em>P. bohemica</em></td>
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<td>.59</td>
<td>.10</td>
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<td>.03</td>
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<td>.025</td>
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<td><em>P. weilii</em> (nom. prov.)</td>
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<td><em>P. hoogshagenii</em></td>
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<td><em>P. liniiformans</em></td>
<td>.16</td>
<td>n/d</td>
<td>.005</td>
<td>Stijve and Kuyper 1985</td>
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</table>
The Toxicity of Psilocybin

- Mice survived 200 mg/kg
- ED50:LD50 ratio of 641 (compare with aspirin - 199, nicotine - 21)

“You would have to eat your own body weight in one sitting to ingest a toxic dose of psilocybe mushrooms.”

— Paul Stamets
Subjective Effects of Psilocybin

This state is marked by:

- Stimulation of affect
- Enhanced ability for introspection
- Similar to dream and hypnogogic states
- Perceptual changes (e.g., illusions, synaesthesias, affective activation and alterations of thought and time)
Subjective Effects of Psilocybin

Characteristics Of The Psychedelic Peak Experience
(Pahnke and Richards, 1966)

- Sense of unity or oneness
- Transcendence of time and space
- Deeply felt positive mood
- Sense of awesomeness and reverence
Subjective Effects of Psilocybin

Characteristics Of The Psychedelic Peak Experience (Pahnke and Richards, 1966)

• Meaningfulness of psychological and/or philosophical insight
• Ineffability
• Paradoxicality
• Transiency
Clinical Research: 1943 - 1973

Dr. Albert Hofmann

Aldous Huxley
“Over a thousand clinical papers were published in the professional literature discussing the experiences of 40,000 patients treated with hallucinogens.”

— Grinspoon and Bakalar, 1979
Clinical Research

Treatment applications included:

- Alcoholism and drug addiction
- Psychosomatic disorders
- Chronic post-traumatic stress
- Obsessive-compulsive disorder
- Anti-social behavior
- Autism
- Existential anxiety in terminal cancer
Hallucinogens for Advanced-Stage cancer anxiety
Patients with Advanced-Stage cancer

- The final months of life are marked by increasing physical and emotional suffering.
- As the patient approaches death, he/she usually experiences various degrees of depression, anxiety, and psychological isolation.
Patients with Advanced-Stage cancer

- The prospect of death often leads to feelings of defeat, helplessness, and despair in members of the patient’s family and attending medical personnel.
- Heroic efforts are frequently undertaken in an attempt to increase the *quantity* of days in the patient’s life.
- Little may be done to enhance the *quality* of intrapersonal and interpersonal life during the final months.
Patients with Advanced-Stage cancer


- Several hundred advanced-stage cancer patients studied
- No preparation
- Superior analgesia compared to hydromorphone and meperidine (several days as opposed to several hours)
- Pain reduced for several weeks
- Theory of “attenuation of anticipation”
- Additional findings included: relief of depression, improved sleep, lessened fear of death
- The occurrence of “happy, oceanic feelings” lasting up to 12 days following treatment.
Patients with Advanced-Stage cancer


- 17 dying patients administered LSD after appropriate therapeutic preparation.
- Variables examined included “tension”, depression, pain and fear of death.
- One-third improved “dramatically”.
- One-third improved “moderately”.
- One-third unchanged.
Patients with Advanced-Stage cancer


“The most dramatic effects came in the wake of a . . . mystical experience.”

- Decrease in fear, anxiety, worry and depression
- Sometimes, need for pain medications lessened mainly because the patient was able to tolerate pain more easily
- Increase in serenity, peace, and calmness
- Decrease in the fear of death
Patients with Advanced-Stage cancer


- 60 terminal cancer patients studied pre and post-treatment.
- 29% dramatically improved
- 41.9% moderately improved
- 22.6% unchanged
- 6.4% had global indexes showing a decrement in post-treatment ratings
Patients with Advanced-Stage cancer

LSD-assisted psychotherapy in patients with terminal cancer. 
International Pharmacopsychiatry 8:129-144

- Changes in the attitude toward and concept of death
- Increased acceptance of death usually followed sessions in which the patients reported deep religious and mystical experiences
- Improvement of the emotional condition and relief of pain frequently observed even after sessions with predominantly psychodynamic content
Current Research with Psilocybin
Clinical Effects of Psilocybin

Positron Emission Tomography and Fluorodeoxyglucose Studies of Metabolic Hyperfrontality and Psychopathology in the Psilocybin Model of Psychosis

F. X. Vollenweider, M.D., K. L. Leenders, M.D., C. Scharfetter, M.D., P. Maguire, Ph.D., O. Stadelmann, Ph.D., and J. Angst, M.D.

The effects of the indolehallucinogen psilocybin, a mixed 5-HT
er agonist, on regional cerebral glucose metabolism were investigated in 10 healthy volunteers with PET and [F-18]-fluorodeoxyglucose (FDG) prior to and following a 15- or 20-mg dose of psilocybin. Psychotomimetic doses of psilocybin were found to produce a global increase in cerebral metabolic rate of glucose (CMRglu) with significant and most marked increases in the frontomedial and frontolateral cortex (24.3%), anterior cingulate (24.9%), and temporomedial cortex (25.3%). Somewhat smaller increases of CMRglu were found in the basal ganglia (18.5%), and the smallest increases were found in the sensorimotor (14.7%) and occipital cortex (14.4%). The increases of CMRglu in the prefrontal cortex, anterior cingulate, temporomedial cortex, and putamen correlated positively with psychotic symptom formation, in particular with hallucinatory ego disintegration. The present data suggest that excessive 5-HT
er receptor activation results in a hyperfrontal metabolic pattern that parallels comparable metabolic findings associated with acute psychotic episodes in schizophrenics and contrasts with the hypofrontality in chronic schizophrenic patients.

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Clinical Effects of Psilocybin

Figure 3. Two [18F]-FDG-PET images of the same subject under baseline (left) and psilocybin (right) conditions. Psilocybin administration (15–20 mg PO) resulted in a global increase of absolute cerebral metabolic rates of glucose (CMRglu; μmol/100 mg/min) with most marked increases in the frontomedial (FRM), frontolateral (FRL), cingulate anterior (CGA), and temporomedial cortices (TEM). Subcortical structures such as the caudate nucleus, putamen, and thalamus were less stimulated than cortical regions. No significant changes were observed in either temporal pole. Red > orange > yellow > green = lowest value of CMRglu; note that the surface of the brain is not color-coded.
Clinical Effects of Psilocybin

Figure 1: Mean Y-BOCS: Baseline & Lowest Score

Figure 2: Mean Y-BOCS vs. Time (all points)

Figure 3: Mean VAS: Baseline & Lowest Score

Figure 4: Mean VAS vs. Time (all points)
Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance

Results Psilocybin produced a range of acute perceptual changes, subjective experiences, and labile moods including anxiety. Psilocybin also increased measures of mystical experience. At 2 months, the volunteers rated the psilocybin experience as having substantial personal meaning and spiritual significance and attributed to the experience sustained positive changes in attitudes and behavior consistent with changes rated by community observers.

Conclusions When administered under supportive conditions, psilocybin occasioned experiences similar to spontaneously occurring mystical experiences. The ability to occasion such experiences prospectively will allow rigorous scientific investigations of their causes and consequences.
Study Methodology & Approval Process
Study Methodology & Approval Process

- 12 subjects
- Metastatic cancer
- Anxiety
- Ages 18 – 70
Exclusion criteria included:

- CNS involvement
- Severe cardiovascular illness
- Treated baseline B.P. > 140/90 mm Hg.
- Abnormal hepatic and renal function
- Diabetes
- Lifetime hx. schizophrenia, bipolar disorder, other psychotic illness
- Anxiety or affective disorder within one year prior to onset of cancer
Study Methodology & Approval Process

Experimental treatment:

- Preparatory psychotherapy
- Double-blind, placebo-controlled methodology
- Niacin 250 mg.
- Psilocybin 0.2 mg/kg
- GCRC setting
- Follow-up evaluation and integration
Study Methodology & Approval Process

Hospital room used for study (Before decorating)
Study Methodology & Approval Process

Hospital room used for study
(After decorating)
### Study Methodology - Instruments

<table>
<thead>
<tr>
<th>Instrument Chart Schedule</th>
<th>2 wks before</th>
<th>1 day before</th>
<th>Just before drug</th>
<th>4 hrs after</th>
<th>6 hrs after</th>
<th>1 day after</th>
<th>2 wks after</th>
<th>monthly X 6 mos</th>
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<tbody>
<tr>
<td>POMS-SR (Profile of Mood States-Brief)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>STAI (Strait Trait Anxiety Inventory)</td>
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<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>BDI (Beck Depression Inventory)</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>SDS (Symptom Distress Scale)</td>
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<td>SD-ASC (Ditrich)</td>
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<td>BPRS (Brief Psychiatric Rating Scale)</td>
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<td>BPI-SF (Brief Pain Inventory-Short Form)</td>
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<td>MSAS (Memorial Symptom Assmt Scale)</td>
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## Study Methodology - Instruments

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<th>4 hrs after</th>
<th>6 hrs after</th>
<th>1 day after</th>
<th>2 wks after</th>
<th>monthly X 6 mos</th>
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<td>MSKCC (Sloan Kettering Pain Card)</td>
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<td>Daily</td>
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<td>X</td>
<td>X</td>
<td>Daily</td>
<td>Daily until 2 wks after</td>
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<td>WHO QOL Bref 26 Qs</td>
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<td>Additional-SRPB 12 Qs</td>
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Advantages Of Psilocybin Over LSD

Psilocybin compared to LSD is:

• Gentler and less intense
• Induces an experience of shorter duration (4-6 hours, compared to LSD’s 8-12 hours)
• Has a stronger visual component
• Induces more euphoria
Psilocybin compared to LSD is:

- Associated with fewer panic reactions
- Less chance of paranoia
- Less negative publicity
- Less likely to impede subject recruitment
Regulatory Hurdles

- FDA
- DEA
- California Research Advisory Panel
- Harbor-UCLA IRB
- Harbor-UCLA GCRC
<table>
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<tr>
<th>Subject #</th>
<th>Age</th>
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<th>Duration Cancer</th>
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<td>54</td>
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<td>Peritoneal Cancer</td>
<td>2 yrs</td>
<td>Liver</td>
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<td>2</td>
<td>58</td>
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<td>Colon Cancer</td>
<td>1 yr</td>
<td>Liver</td>
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<td>3</td>
<td>57</td>
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<td>Colorectal Cancer</td>
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<td>Lymphatic, Liver</td>
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<td>6</td>
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<td>Breast Cancer</td>
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<td>7</td>
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<td>11</td>
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<td>2 yrs</td>
<td>Liver, Lung, Bone</td>
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<td>13</td>
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<td>Female</td>
<td>Multiple Myeloma</td>
<td>8 yrs</td>
<td>Abdomen, Tongue, Vagina</td>
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</table>
Heart Rate and Blood Pressure

- Heart Rate (bpm)
- Time (hours)

- Placebo
- Psilocybin 0.2 mg/kg

**p<0.01
Heart Rate and Blood Pressure

Systolic
- Placebo
- Psilocybin 0.2 mg/kg

Diastolic

*p<0.05, **p<0.01
### 24-Hour Cardiac Monitor

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<th>Subject #</th>
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<th>Placebo (Niacin 250 mg)</th>
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<td>2</td>
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<td>332</td>
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<td>7</td>
<td>24</td>
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<td>13</td>
<td>0</td>
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<td>0</td>
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<td>192</td>
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<td>364</td>
<td>4</td>
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<td>49</td>
<td>29</td>
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<td>10</td>
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<td>11</td>
<td>875</td>
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<tr>
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<td>5</td>
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<td>2</td>
<td>10</td>
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<tr>
<td></td>
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<td></td>
<td>(one 3-beat run @15:27)</td>
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</table>
5D-ASC

![Graph showing 5D ASC Scale results for Placebo and Psilocybin 0.2 mg/kg.](image)

- OB
- AED
- VR
- AA
- RV

% Maximum Score

- Placebo
- Psilocybin 0.2 mg/kg

* \( p < 0.05 \)
** \( p < 0.01 \)
5D-ASC Subscales

- Positive derealization
- Altered sense of time
- Mania-like experience
- Thought disorder
- Thought disorder
- Delusion
- Fear of loss of thought control
- Elementary hallucinations
- Visual pseudohallucinations
- Synesthesia
- Changed meaning of percepts
- Facilitated recollection
- Facilitated imagination

* Placebo
* Psilocybin 0.2 mg/kg

*p<0.05
Beck Depression Inventory

Assessment Time Point

- 1 Day Before
- 1 Day After
- 2 Weeks After

BDI Score

- Placebo
- Psilocybin

Assessment Time Point

1 Day Before 1 Day After 2 Weeks After
Beck Depression Inventory

BDI Score

1 Day Before  Month 1  Month 2  Month 3  Month 4  Month 5  Month 6

*p < 0.05
**STAI State**

**STAI State Anxiety Score**

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>Psilocybin</th>
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<tbody>
<tr>
<td>1 Day Before</td>
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<tr>
<td>6 Hours After</td>
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<td>1 Day After</td>
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<td>2 Weeks After</td>
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**STAI State Score**

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>Psilocybin</th>
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<tbody>
<tr>
<td>1 Day Before</td>
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<td>Month 1</td>
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<td>Month 6</td>
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</table>
STAI Trait

STAI Trait Anxiety Score

1 Day Before  6 Hours After  1 Day After  2 Weeks After

Placebo ○ Psilocybin 0.2 mg/kg

** *  
\( p < 0.05, \quad ** p < 0.01 \)
Study Results

ONLINE FIRST
Pilot Study of Psilocybin Treatment for Anxiety in Patients With Advanced-Stage Cancer

Charles S. Grab, MD; Alicia L. Danforth, MA; Gurpreet S. Chopra, MD; Marycie Hagerty, RN, BSN, MA; Charles R. McKay, MD; Adam L. Halberstadt, PhD; George R. Greer, MD

Context: Researchers conducted experiments with hallucinogens in the 1950s and 1970s, however, political and cultural factors led to the cessation of all projects. This implies a potentially promising clinical use of hallucinogens in the treatment of anxiety in advanced-stage cancer.

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

Design: A double-blind, placebo-controlled study of patients with advanced-stage cancer and anxiety, with subjects acting as their own control, using a moderate dose (0.2 mg/kg) of psilocybin.

Setting: A clinical research unit within a large public-sector academic medical center.

Participants: Twelve adults with advanced-stage cancer and anxiety.

Main Outcome Measures: In addition to monitoring safety and subjective experience before and during experimental treatment sessions, follow-up data including results from the Beck Depression Inventory, Profile of Mood States anxiety subscale demonstrated a significant reduction in anxiety at 1 and 3 months after treatment. The Beck Depression Inventory revealed an improvement of mood that reached significance at 6 months; the Profile of Mood States identified mood improvement after treatment with psilocybin that approached but did not reach significance.

Conclusions: This study established the feasibility and safety of administering moderate doses of psilocybin to patients with advanced-stage cancer and anxiety. Some of the data revealed a positive trend toward improved mood and anxiety. These results support the need for more research in this long-neglected field.

Trial Registration: clinicaltrials.gov Identifier: NCT00302744

Arch Gen Psychiatry. Published online September 6, 2010. doi:10.1001/archgenpsychiatry.2010.116

Clinical Effects of Psilocybin

Rapid and sustained symptom reduction following psilocybin treatment for anxiety and depression in patients with life-threatening cancer: a randomized controlled trial

Stephen Ross\textsuperscript{1,2,3,4,5,6}, Anthony Bossis\textsuperscript{1,2,4}, Jeffrey Guss\textsuperscript{1,2,4}, Gabrielle Agin-Liebes\textsuperscript{10}, Tara Malone\textsuperscript{1}, Barry Cohen\textsuperscript{7}, Sarah E Mennenga\textsuperscript{1}, Alexander Belser\textsuperscript{9}, Krystallia Kalliontzi\textsuperscript{2}, James Babb\textsuperscript{9}, Zhe Su\textsuperscript{3}, Patricia Corby\textsuperscript{2} and Brian L Schmidt\textsuperscript{2}

Abstract

Background: Clinically significant anxiety and depression are common in patients with cancer, and are associated with poor psychiatric and medical outcomes. Historical and recent research suggests a role for psilocybin to treat cancer-related anxiety and depression.

Methods: In this double-blind, placebo-controlled, crossover trial, 29 patients with cancer-related anxiety and depression were randomly assigned and treated with psilocybin 100 mg and placebo, and depression was assessed with self-report and clinical measures. The primary outcome was change in depression, assessed with the Montgomery-Åsberg Depression Rating Scale.

Results: Significant reductions in psychological symptoms were observed in patients receiving psilocybin. The median decrease in the Montgomery-Åsberg Depression Rating Scale was 21 points (95% CI 15.0 to 32.6; p < 0.001).

Conclusion: Psilocybin may be an effective treatment for cancer-related anxiety and depression.
Clinical Effects of Psilocybin

Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial

Roland R Griffiths¹,², Matthew W Johnson¹, Michael A Carducci³, Annie Umbricht¹, William A Richards¹, Brian D Richards¹, Mary P Cosimano¹ and Margaret A Klinedinst¹

Abstract
Cancer patients often develop chronic, clinically significant symptoms of depression and anxiety. Previous studies suggest that psilocybin may decrease depression and anxiety in cancer patients. The effects of psilocybin were studied in 51 cancer patients with life-threatening diagnoses and symptoms of depression and/or anxiety. This randomized, double-blind, cross-over trial investigated the effects of a very low (placebo-like) dose (1 or 3 mg/70 kg) vs. a high dose (22 or 30 mg/70 kg) of psilocybin administered in counterbalanced sequence with 5 weeks between sessions and a 6-month follow-up.
“Death must become a more human experience. To preserve the dignity of death and prevent the living from abandoning or distancing themselves from the dying is one of the great dilemmas of modern medicine”.

Harbor-UCLA Psilocybin Research:

www.clinicaltrials.gov

www.heffter.org
FUTURE CHALLENGES

- Implement the lessons of the past
- Optimize safety
- Strengthen ethical standards
- Prioritize public health implications
- Respond to need for greater diversity
- Navigate regulatory obstacles
- Assess funding options carefully