No. 21-70544

In the United States Court of Appeals for the Ninth Circuit

ADVANCED INTEGRATIVE MEDICAL SCIENCE INSTITUTE, PLLC, DR. SUNIL AGGARWAL, MD, PHD, MICHAL BLOOM, AND ERINN BALDESCHWILER,

Petitioners,

v.

U.S. DRUG ENFORCEMENT ADMINISTRATION; MERRICK GARLAND, IN HIS OFFICIAL CAPACITY AS ATTORNEY GENERAL; AND D. CHRISTOPHER EVANS, IN HIS OFFICIAL CAPACITY AS ACTING ADMINISTRATOR OF THE U.S. DRUG ENFORCEMENT ADMINISTRATION,

Respondents.

PETITIONERS' EXCERPTS OF RECORD
VOLUME 1 OF 1

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621 SW Morrison St., Suite 900, Portland, OR 97205

January 15, 2021

VIA E-MAIL (*dea.registration.help@usdoj.gov*) **AND U.S. FIRST CLASS REGISTERED MAIL**

Drug Enforcement Administration
Attn: Regulatory Section/DRG
8701 Morrissette Drive
Springfield, VA 22152

Dear DEA Regulatory Section:

The Advanced Integrative Medical Science Institute (AIMS) is an integrative oncology clinic located in Seattle, WA. I am counsel to the clinic and its co-director, Dr. Sunil Aggarwal. Dr. Aggarwal is a palliative care specialist who treats patients with advanced cancer. He holds a DEA registration to prescribe controlled substances (DEA # FA4274926). Dr. Aggarwal seeks additional registration to obtain psilocybin, a Schedule I drug (code 7437), for therapeutic use with terminally ill cancer patients suffering anxiety and/or depression. This registration is sought pursuant to the Washington and U.S. Right to Try (RTT) Acts.[1] This letter provides background information about the RTT, and we seek your guidance on how DEA will accommodate RTT so that Dr. Aggarwal and the AIMS Institute can obtain psilocybin for therapeutic use with terminally ill patients.

Brief Background on Psilocybin's Utility in Relief of Anxiety and Depression in Terminally Ill Patients

Medical research demonstrates the powerful therapeutic uses of psilocybin in the treatment of anxiety and depression associated with terminal illness. Patients with advanced cancer suffering from treatment resistant anxiety and/or depression experience significant reductions in both anxiety and depression, and improvements of mood, following a single guided treatment with psilocybin, with no safety concerns or clinically significant adverse events.[2] This is important because people experiencing late stage terminal disease experience

[1] RCW 69.77 et seq; 21 U.S.C.A. § 360bbb-0a.

[2] Grob et al., *Pilot study of psilocybin treatment for anxiety in patients with advanced- stage cancer*, 68 ARCH GEN PSYCHIATRY 71, 71 (2011) (anxiety levels measured at one, three, and six months after treatment "demonstrated a sustained reduction in anxiety"); Griffiths et al., *Psilocybin Produces Substantial and Sustained Decreases in Depression and Anxiety in Patients With Life-Threatening Cancer: A Randomized Double-Blind Trial,* 30 J. Psychopharmacology 1181, 1195 (2016) (single dose of psilocybin produced large and significant decreases in depression, anxiety or mood disturbance, and increases in measures of quality of life, life meaning, death acceptance, and optimism in patients with a life-threatening cancer diagnosis; effects sustained at 6 months.); Johnson & Griffiths, *Potential Therapeutic Effects of Psilocybin*, 30 Neurotherapeutics 734, 734 (2017); Ross S., *Therapeutic use of classic psychedelics to treat cancer-related psychiatric distress.* Int Rev Psychiatry, 2018 Aug;30(4):317-330. doi: 10.1080/09540261.2018.1482261. Epub 2018 Aug 13(review of clinical trials from 1960-2018 researching therapeutic use of psychedelic treatment in patients with serious or terminal illnesses and related psychiatric illness; psychedelic-assisted treatment can produce rapid, robust, and sustained improvements

emotional suffering to a greater extent than those in the general population.[3] Dying patients frequently suffer depression and anxiety.[4] For such patients, psychotherapy facilitated with psychedelics may provide much needed relief: *"People in the psychedelic trip often experience being at one with the world or even the universe. It's as if they have died, as if they've gone out to another place. They exist beyond their body. That experience can give them a sense of perpetuity, of permanence, of being part of the cycle of life, which of course we all are."*[5] Patients able to access psychedelic therapy express compelling positive experiences: *"I felt like I was being shown what happens after [death], like an afterlife. I'm not a religious person and I'd be hard pushed to say I was anything near spiritual either, but I felt like I'd experienced some of that, and experienced the feeling of an afterlife, like a preview almost, and I felt totally calm, totally relaxed, totally at peace. So that when that time comes for me, I will have no fear of it at all."*[6] This is great news as: "Anxiety is one of the most common reasons for psychiatric consultation in terminally ill cancer patients and has been linked to lower levels of quality of life, increased levels of insomnia, decreased trust in physicians, and poor treatment compliance."[7]

The Right to Try

The state and federal "Right to Try" (RTT) acts[8] are statutes intended to allow terminally ill patients access to drugs still in investigational stages, recognizing that such patients do not have the luxury of time to await the slow process of new drug approval. Psilocybin qualifies as such a drug.[9]

To qualify as an eligible investigational drug ("EID") under the federal RTT, a drug must satisfy four requirements. First, it must have completed an FDA-approved Phase I clinical trial.[10] Second, the drug must not be approved or licensed for any use through the federal Food, Drug, and Cosmetic Act ("FD&C Act") or the

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in cancer-related psychological and existential distress.) See also, *Individual Experiences in Four Cancer Patients Following Psilocybin-Assisted Psychotherapy,* Pharmacol., 03 April 2018 (participants with anxiety, depression, and other existential distress achieved relief with psilocybin treatment, and benefits were sustained throughout follow-up). https://www.frontiersin.org/articles/10.3389/fphar.2018.00256/full. See generally, M. Pollan, *How to Change Your Mind* (2018); Lauren Slater, *How Psychedelic Drugs Can Help Patients Face Death*, NEW YORK TIMES MAGAZINE (Apr. 20, 2012), ("[T]he results showed that administering psilocybin to terminally ill subjects could be done safely while reducing the subjects' anxiety and depression about their impending deaths.").

[3] *See, e.g.*, H. Chochinov, *Psychiatry and Terminal Illness*, 45 Can. .J. Psychiatry 413,146– 48 (2000); W. Lichtenthal et al., *Do Rates of Mental Disorders and Existential Distress Among Advanced Stage Cancer Patients Increase as Death Approaches?* 18 Psycho-Oncology 50, 54 (2009); A. Mitchell et al., *Prevalence of Depression, Anxiety, and Adjustment Disorder in Oncological, Haematological, and Palliative-Care Settings: A Meta-Analysis of 94 Interview-Based Studies*, 12 Lancet Oncology 160, 167 tbl.2 (2011).

[4] Research shows that 18% of terminally ill cancer patients experience moderate anxiety, while 12% suffer severe anxiety. E. Kolva, et al. Anxiety in Terminally Ill Cancer Patients, *42(5)* Journal of Pain and Symptom Management, 691 – 701 (2011).

[5] Id.

[6] Id.

[7] E. Kolva, et al., *Anxiety in Terminally Ill Cancer Patients,* 42*(5)* J. Pain and Sympt. Management*,* 691 – 701 (2011).

[8] RCW 69.77 et seq; 21 U.S.C.A. § 360bbb-0a.

[9] See supra n. 2, citing clinical trial studies with psilocybin. See also, Usona Institute, Investigator's Brochure https://www.usonainstitute.org/wp-content/uploads/2020/08/Usona_Psilocybin_IB_V3.0_08.31.2020_cc.pdf; https://clinicaltrials.gov/ct2/results?cond=&term=psilocybin&cntry=&state=&city=&dist=.

[10] 21 U.S.C. § 360bbb-0a(a)(2)(A).

Public Health Services Act ("PHSA").[11] Third, the drug must either: (a) have an application filed under the FD&C Act or PHSA, or (b) be under investigation in a clinical trial that is "intended to form the primary basis of a claim of effectiveness in support of approval" and be the subject of an active IND application under the FD&C Act or PHSA.[12] Fourth, the drug's active development and production must be ongoing, not discontinued by the manufacturer, and not subject to a clinical hold.[13] Similarly, under the Washington RTT, a drug is "investigational" when it has successfully completed Phase 1 and is currently in a subsequent phase of an FDA-approved clinical trial assessing its safety.[14] Psilocybin meets all of these requirements.

The AIMS Institute intends to purchase psilocybin from Organix, a company which holds an IND for this drug and is registered as a Distrubuter of this drug.[15] It is clearly within the intention of the RTT to allow this, even though psilocybin is a Schedule I drug. This is evident as neither the U.S. RTT nor the Washington State RTT exclude Schedule I substances from their scope.[16]

Issuance of a registration to enable Dr. Aggarwal to obtain psilocybin for the intended purpose is fully consistent with the public interest. None of the public interest factors that might counsel against issuance of a registration are present.[17]

The underlying scope of authority by the DEA is limited to effectuating controls against diversion of controlled substances, and not determinations of the practice of medicine. *Gonzales v. Oregon*, 126 S.Ct. 904.

I look forward to your guidance as to how DEA will accommodate RTT so that Dr. Aggarwal and the AIMS Institute can obtain psilocybin for therapeutic use with terminally ill patients. The existing DEA forms do not appear to accommodate the RTT, which may be due to the fact that it was relatively recently enacted; hence it is confusing to use the existing forms for this purpose. Should Dr. Aggarwal seek registration as a "researcher", though his intention is therapeutic use as a palliative care clinician, treating terminally ill patients, not a "researcher" in the traditional sense? If not a researcher registration, how ought we proceed?

In the interest of the terminally ill patients with refractory anxiety and/or depression, we hope DEA can promptly advise on how to proceed.

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[11] *Id*. § 360bbb-0a(a)(2)(B). Specifically, the drug may not be approved or licensed for any use under Section 355 of the FD&C Act or Section 351 of the PHSA.

[12] *Id.* § 360bbb-0a(a)(2)(C). Specifically, the application in (1) must be under Section 355(b) of the FD&C Act or Section 351(a) of the PHSA. For brevity's sake, "IND application" in this memo means anything meeting these criteria.

[13] *Id*. § 360bbb-0a(a)(2)(D).

[14] RCW 69.77.020(4).

[15] Organix, Inc. 240 Salem Street, Woburn, MA 01801 www.organixinc.com

[16] In contrast, some RTT statutes explicitly exclude Schedule I substances from RTT shelter. For example, Missouri's RTT statute, in defining what qualifies as an "investigational drug", states that an "Investigational drug …**shall not include Schedule I controlled substances.")** Revised Statutes of Missouri, Section 191.480(2014) (2)(emphasis added). Compare: RCW 69.77.020((4) "Investigational product" means a drug, biological product, or device that has successfully completed phase one and is currently in a subsequent phase of a clinical trial approved by the United States Food and Drug Administration assessing the safety of the drug….").

[17] The only pertinent factor relates to assuring effective controls against diversion. Effective controls can and will be established at AIMS, which already stores controlled substances.

Respectfully submitted,

Kathryn Tucker

Kathryn L. Tucker

Counsel to AIMS Institute and Dr. Sunil Aggarwal

Cc via email: Heather Danner-Ryan, Group Supervisor, Diversion Group 1, New England Field Division, Boston Heather.A.Danner-Ryan@usdoj.gov

Edwin Dizon, Diversion Investigator, Seattle Field Division Edwin.S.Dizon@usdoj.gov

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Drug Enforcement Administration
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www.dea.gov

Kathryn L. Tucker, Esq.
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Portland, Oregon 97205
kathryn@emergelawgroup.com

Dear Kathryn Tucker:

This letter is in response to your letter dated January 15, 2021, to the Drug Enforcement Administration (DEA). In your letter you state that you are counsel to Advanced Integrative Medical Science Institute and its co-director, Sunil Aggarwal, M.D. You state that Dr. Aggarwal is a palliative care specialist who treats patients with advanced cancer and currently holds a DEA registration as a practitioner. Dr. Aggarwal seeks additional authorization or additional registration (from DEA) to obtain psilocybin, a schedule I controlled substance, for therapeutic use for terminally ill cancer patients suffering anxiety and/or depression. You state that Dr. Aggarwal seeks such authorization pursuant to the "Right to Try Act" (RTT), officially designated as the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017. You ask DEA for guidance on how DEA will accommodate the RTT, so that Dr. Aggarwal may obtain psilocybin for therapeutic use with terminally ill patients. DEA appreciates the opportunity to address your request.

DEA understands and appreciates the intent of the RTT, that is, to provide easier access to experimental drugs to patients afflicted with terminal illness. However, absent an explicit statutory exemption to the Controlled Substances Act (CSA), DEA has no authority to waive any of the CSA's requirements pursuant to the RTT. As is made clear in 21 U.S.C. 360bbb-0a(b), excerpted below, the RTT does not waive the requirements of any provision of the Controlled Substances Act (CSA) or its implementing regulations.

> *(b) Exemptions*
>
> *Eligible investigational drugs provided to eligible patients in compliance with this section are exempt from sections 352(f), 353(b)(4), 355(a), and 355(i) of this title, section 351(a) of the Public Health Service Act, and parts 50, 56, and 312 of title 21, Code of Federal Regulations (or any successor regulations), provided that the sponsor of such eligible investigational drug or any person who manufactures, distributes, prescribes, dispenses, introduces or delivers for introduction into interstate commerce, or provides to an eligible patient an eligible investigational drug pursuant to this section is in compliance with the applicable requirements set forth in sections 312.6, 312.7, and 312.8(d)(1) of title 21, Code of Federal Regulations (or any successor regulations) that apply to investigational drugs.*

A potential avenue for Dr. Aggarwal to pursue is to apply for a schedule I researcher registration with DEA to conduct research with psilocybin, a schedule I controlled substance. The procedures for such application are outlined in 21 U.S.C. 823(f), 21 CFR 1301.18, and 21 CFR 1301.32.

Finally, in your email to DEA, sent on February 2, 2021, you inquire as to the possibility of DEA issuing an exemption from prosecution to Dr. Aggarwal. You state in your email that this would be akin to the exemption provided for in 21 CFR 1316.24, titled, "Exemption from prosecution for researchers." The exemption provided in this regulation, however, only applies to individuals already registered with DEA to engage in research in controlled substances. *See* 21 CFR 1316.24(a) ("Upon registration of an individual to engage in research in controlled substances . . . the Administrator . . . may exempt the registrant when acting within the scope of his registration, from prosecution . . ."). It would therefore not be applicable to Dr. Aggarwal at this time. Should Dr. Aggarwal obtain a schedule I researcher registration from DEA, he may then petition the DEA Administrator for a grant of exemption from prosecution following the procedure set forth in 21 CFR 1316.24(b).

I trust this letter adequately addresses your inquiry. For additional information regarding the DEA Diversion Control Division, please visit www.DEAdiversion.usdoj.gov. If you have additional questions regarding this issue, please contact the Policy Section at (571) 362-3260.

Sincerely,

Thomas W. Prevoznik
Deputy Assistant Administrator
Diversion Control Division

No. 21-70544

In the United States Court of Appeals for the Ninth Circuit

ADVANCED INTEGRATIVE MEDICAL SCIENCE INSTITUTE, PLLC, DR. SUNIL AGGARWAL, MD, PHD, MICHAL BLOOM, AND ERINN BALDESCHWILER,

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Respondents.

DECLARATION OF MICHAL BLOOM, IN SUPPORT OF MOTION FOR EXPEDITED REVIEW

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Attorneys for Petitioners

1. My name is Michal Bloom. I am one of the Petitioners challenging the denial by the DEA of therapeutic use of psilocybin, an investigational drug shown to be safe and effective in relieving anxiety and depression in patients with advanced illness. I live in Seattle, Washington. I am now retired, due to disability caused by my medical condition. I formerly practiced law as an attorney; my career was with the United States Trustee Program, within US Department of Justice.

2. I have advanced, recurrent, BRCA+, ovarian cancer with metastasis to my lymph nodes. I was first diagnosed in February 2017. Since then I have undergone several surgeries, and several rounds of chemotherapy for treatment of the cancer. I have also had surgery to install a port for chemotherapy in my chest. I have had a wide range of distressing symptoms related to my medical condition, including enduring treatment while placed on table which turned upside down. I have had to manage side effects of various treatment, including persistent recurrent intestinal distress; terrible constipation and recurring bowel obstruction; chronic fatigue; weakness; hospitalization for an infected port; enduring an episode with MRSA; I have experienced the distress of having open wounds for months.

3. I am receiving care at the Advanced Integrative Medical Science ("AIMS") Institute, an integrative oncology clinic in Seattle. Dr. Sunil Aggarwal, who practices at AIMS, is my palliative care physician. I have been advised and understand that my medical condition is serious, advanced and life threatening. I

understand that I may have a very limited quantum of time to live. I do not have the luxury of time to await the full FDA new drug approval process to run its course to access a promising investigational drug.

4. I experience severe anxiety and depression, which approved therapies, have not ameliorated.

5. I have heard and read about clinical trials with the investigational drug psilocybin as a tool for relief of anxiety and depression in patients with life-threatening illnesses. I have discussed this possible therapy with Dr. Aggarwal. I have been advised of the possible risks and benefits of trying this investigational drug. I decided I wanted to try it and I completed an Informed Consent document as specified in Washington's Right to Try law. A true and complete copy of this document is attached hereto as **Exhibit A.** I want to be able to have therapy facilitated with psilocybin under provisions of the Right to Try law, in the care of Dr. Aggarwal.

6. I have tried a variety of treatment modalities in the effort to mitigate my anxiety and depression, including ketamine-assisted psychotherapy.

7. However, I have not gotten relief with conventional, and even cutting edge and somewhat unconventional, medications or modalities. I have experienced a lot of suffering from unrelieved anxiety and depression.

8. I hope Dr. Aggarwal can obtain psilocybin for therapeutic use in treatment of my anxiety and depression. Because of my advanced cancer it is

possible that I have little time to live; if I am to benefit from this therapy it is urgent that I be able to have access soon. I believe this is the intention of the Right to Try law. I believe that I have a right to try the investigational drug psilocybin, for relief of severe anxiety and depression.

9. It is my hope that therapy facilitated with psilocybin will allow me to obtain relief from the debilitating anxiety and depression I endure. I believe psilocybin assisted therapy could improve my quality of life and aid in my overall longevity.

****

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I declare under penalty of perjury that the foregoing is true and correct.

Executed on March 26, 2021.

Michal Bloom

REQUEST FOR INVESTIGATIONAL PRODUCT INFORMED CONSENT FORM

Sunil K. Aggarwal, MD, PhD, FAAPMR	**Treating Physician**	**AIMS Institute**	**(206) 420-1321**

We are required by law to provide the following information to you.

You have been diagnosed with advanced cancer.

The currently approved products and treatments for advanced cancer include chemotherapy, immunotherapy, and radiation therapy. All currently approved and conventionally recognized treatments are unlikely to prolong your life.

You are seeking to use the investigational product Psilocybin ([3-[2-(dimethylamino)ethyl]-1H-indol-4-yl] dihydrogen phosphate (IND# 129532; Sponsor Usona Institute).

The potentially best outcome of completing a program of psilocybin assisted therapy is that it substantially and robustly palliates or relieves your depressive and anxious symptoms for more than a year, and that this improvement leads to improved immune function and potential modification, slowing, or reversal of the advancement of cancer.

The potentially worst outcome of completing a program of psilocybin assisted therapy is that you experience mild headache, dizziness, fatigue, fainting, or worsening anxiety. There is the possibility that new, unanticipated, different, or worse symptoms may result and that death could be hastened by the proposed treatment.

Realistically, the most likely outcome is that you would experience prolonged relief of depressive and anxiety symptoms and better capacity to cope with your illness.

Please note that your health benefit plan is not obligated to pay for the investigational product or any harm caused to you by psilocybin, unless otherwise specifically required to do so by law or contract, and that in order to receive psilocybin you may be required to pay the costs of administering it.

Please note that you are liable for all expenses consequent to the use of psilocybin, except as otherwise provided in your health benefit plan or a contract between yourself and Usona Institute.

SIGNATURE PAGE

I voluntarily consent to this request.

_____
Name of Eligible Patient (Please Print)

_____ _____
Signature of Eligible Patient Date

_____
Name of Witness (Please Print)

_____ _____
Signature of Witness Date

_Sunil Aggarwal, MD, PhD, FAAPMR_____
Name of Treating Physician

_____ _____10/31/20_____
Signature of Treating Physician Date

J. Michael Bloom
Name of Eligible Patient (Please Print)

Signature of Eligible Patient

11/24/20
Date

Stacey McIntyre
Name of Witness (Please Print)

Signature of Witness

11/24/20
Date

Sunil Aggarwal, MD, PhD, FAAPMR
Name of Treating Physician

Signature of Treating Physician

Date

No. 21-70544

In the United States Court of Appeals for the Ninth Circuit

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Respondents.

DECLARATION OF ERINN BALDESCHWILER, IN SUPPORT OF MOTION FOR EXPEDITED REVIEW

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hmartinez@perkinscoie.com

Attorneys for Petitioners

1. My name is Erinn Baldeschwiler. I am one of the Petitioners challenging the denial by the DEA of therapeutic use of psilocybin, an investigational drug shown to be safe and effective in relieving anxiety and depression in patients with advanced illness. I live in La Conner, Washington. I am the mother of two children.

2. I was diagnosed in 2020 with Stage IV metastatic breast cancer, at the age of 48. I have had multiple tumors in my neck, chest, lymph nodes, adrenal glands, left breast, lung, ovary, and bones.

3. I am receiving care at the Advanced Integrative Medical Science (AIMS) Institute, an integrative oncology clinic in Seattle. Dr. Sunil Aggarwal, who practices at AIMS, is my palliative care physician. I have been advised and understand that my medical condition is serious, advanced and life threatening. I understand that I may have a very limited quantum of time to live. I do not have the luxury of time to await the full FDA new drug approval process to run its course to access a promising investigational drug.

4. The prospect of dying soon and not being here to watch my children grow up, and to nurture them to adulthood causes me severe anxiety and depression, which conventional therapy has not ameliorated.

5. I have heard and read about clinical trials with the investigational drug psilocybin as a tool for relief of anxiety and depression in patients with life-threatening illnesses. I have discussed this possible therapy with Dr. Aggarwal. I

have been advised of the possible risks and benefits of trying this investigational drug. I decided I wanted to try it and I completed an Informed Consent document as specified in Washington's Right to Try law. A true and complete copy of this document is attached hereto as **Exhibit A**. I want to be able to have therapy facilitated with psilocybin under provisions of the Right to Try law, in the care of Dr. Aggarwal.

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9. It is my hope that therapy facilitated with psilocybin will allow me to obtain relief from the debilitating anxiety and depression I endure. I believe psilocybin assisted therapy could improve my quality of life and aid in my overall longevity.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on March 25, 2021.

Efinn Baldeschwiler

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Sunil K. Aggarwal, MD, PhD, FAAPMR	**Treating Physician**	**AIMS Institute**	**(206) 420-1321**

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Please note that you are liable for all expenses consequent to the use of psilocybin, except as otherwise provided in your health benefit plan or a contract between yourself and Usona Institute.

SIGNATURE PAGE

I voluntarily consent to this request.

Erinn Baldeschwiler
Name of Eligible Patient (Please Print)

Signature of Eligible Patient

11/1/2020
Date

Valerie Pierson
Name of Witness (Please Print)

Valerie Pierson
Signature of Witness

11/1/2020
Date

Sunil Aggarwal, MD, PhD, FAAPMR
Name of Treating Physician

Sunil K Aggarwal
Signature of Treating Physician

10/31/20
Date

No. 21-70544

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Petitioners,

v.

U.S. DRUG ENFORCEMENT ADMINISTRATION; MERRICK GARLAND, IN HIS OFFICIAL CAPACITY AS ATTORNEY GENERAL; AND D. CHRISTOPHER EVANS, IN HIS OFFICIAL CAPACITY AS ACTING ADMINISTRATOR OF THE U.S. DRUG ENFORCEMENT ADMINISTRATION,

Respondents.

DECLARATION OF DR. SUNIL AGGARWAL IN SUPPORT OF MOTION FOR EXPEDITED REVIEW

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1. I am the Co-Founder and Co-Director of the the Advanced Integrative Medical Science (AIMS) Institute, PLLC, a professional limited liability corporation. AIMS is an integrative oncology clinic located in Seattle, WA, dedicated to providing cutting edge integrative medical care, research, and education in oncology, psychiatry, neurology, rehabilitation, pain and palliative care.

2. I am a physician licensed to practice medicine in the State of Washington and am in good standing. I completed my medical degree at the University of Washington in 2010, I also received a PhD in Geography from the University of Washington, in 2008. I was a member of the NIH-funded Medical Scientist Training Program and received additional funding through the National Science Foundation Graduate Research Fellowship. I hold undergraduate degrees in Philosophy (B.A. – With Distinction) and Chemistry (B.S. – High Honors) from the University of California, Berkeley, both received in 2001. I hold a license to prescribe controlled substances issued to me by the Drug Enforcement Administration for drugs listed in Schedules II-V.

3. I completed an internship in Internal Medicine at Virginia Mason Medical Center, in Seattle; a Residency in Physical Medicine and Rehabilitation at NYU Medical Center, in New York; and a clinical fellowship in Hospice and Palliative Medicine at the NIH Clinical Center for Pain and Palliative Care Service in Bethesda, MD.

4. I am board-certified in both Physical Medicine and Rehabilitation and Hospice and Palliative Medicine. I hold faculty appointments at the University of Washington School of Medicine and Bastyr University. I am a hospice and palliative medicine and physical medicine and rehabilitation physician and medical geographer.

5. My primary clinical work is as an Integrative Pain Management and Palliative Care Clinician in private practice at the AIMS Institute ("AIMS"). I also serve as an on-call Palliative Care Physician and Associate Medical Director of MultiCare Hospice, in Tacoma, WA. I

previously ran the palliative care medicine consultation service at the MultiCare Auburn hospital and regional cancer center.

6. I have received honors and awards for my work. For example, in March 2020, I was recognized as a Top 20 Emerging Leader in Hospice and Palliative Medicine by the American Academy of Hospice and Palliative Care.

7. Many patients I provide care to at AIMS are primarily in last stages of cancer. Many suffer with anxiety and depression. I provide a variety of treatment modalities to try to mitigate these patients' anxiety and depression.

8. Some of my patients do not respond to therapy with conventional, and even cutting edge and somewhat unconventional, medications or modalities. At any given time, I have a roster of patients suffering with anxiety and depression that cannot be relieved with approved therapies. I am familiar with the medical literature reflecting that for terminally ill patients suffering unrelieved anxiety and/or depression, quality and quantity of life is often reduced.

9. I have followed the clinical trials with the investigational drug psilocybin as a tool for relief of anxiety and depression in patients with life-threatening illnesses with keen interest.[1] I am aware that psilocybin has successfully completed Phase I clinical trials and remains under investigation in later stage clinical trials. In my opinion, it would be beneficial to some of my patients who have advanced stage cancer to have access to psilocybin therapy. I have discussed the possibility of psilocybin therapy with some of my patients, including Erinn Baldeschwiler and Michal Bloom.

[1] **Exhibit A** attached hereto includes two studies regarding the clinical utility of psilocybin for therapeutic use, including: Charles S. Grob, Alicia L. Danforth, & Gurpreet S. Chopra, , *Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer*, 68 ARCH GEN PSYCHIATRY 71, 71 (2011) (anxiety levels measured at one, three, and six months after treatment "demonstrated a sustained reduction in anxiety"); Roland R. Griffiths *et al*., *Psilocybin produces substantial and sustained decreases in depression and anxiety in patients with life-threatening cancer: A randomized double-blind trial*, 30 J. OF PSYCHOPHARMACOLOGY 1181, 1195 (2016).

10. I have investigated various ways of obtaining the investigational drug psilocybin for therapeutic use with my patients, recognizing that it is a Schedule I controlled substance. It is my understanding that I would violate the law if I were to obtain, possess or administer a Schedule I substance without clear permission from the federal and state drug enforcement authorities. I have also previously explored "Expanded Access" as a method of obtaining a Schedule I controlled substance for patients in urgent need for an eligible investigational drug. My experience with Expanded Access did not result in any access to the Schedule I drug. In my experience, Expanded Access was an unworkable process for my terminally ill patients with an urgent need for an eligible investigational drug, and this view is informed by an unsuccessful attempt to utilize this process in the recent past.

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I declare under penalty of perjury that the foregoing is true and correct.

Executed on March 25, 2021.

Sunil Aggarwal, MD, PhD, FAAPMR

ORIGINAL ARTICLE

ONLINE FIRST

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

Charles S. Grob, 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 extensive investigations of hallucinogens in the 1950s and 1960s. By the early 1970s, however, political and cultural pressures forced the cessation of all projects. This investigation reexamines a potentially promising clinical application of hallucinogens in the treatment of anxiety reactive to advanced-stage cancer.

Objective: 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, and State-Trait Anxiety Inventory were collected unblinded for 6 months after treatment.

Results: Safe physiological and psychological responses were documented during treatment sessions. There were no clinically significant adverse events with psilocybin. The State-Trait Anxiety Inventory trait 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

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IN RECENT YEARS, THERE HAS BEEN a growing awareness that the psychological, spiritual, and existential crises often encountered by patients with cancer and their families need to be addressed more vigorously.[1-4] From the late 1950s to the early 1970s, research was carried out exploring the use of hallucinogens to treat the existential anxiety, despair, and isolation often associated with advanced-stage cancer.[5-15] Those studies described critically ill individuals undergoing psychospiritual epiphanies, often with powerful and sustained improvement in mood and anxiety as well as diminished need for narcotic pain medication. Despite these promising results, there has been no follow-up research.

Today, the medical value of hallucinogens is again being examined in formal psychiatric settings. One substance under investigation is psilocybin, 4-phosphoryloxy-*N*,*N*-dimethyltryptamine, which occurs in nature in various species of mushrooms. Psilocybin is rapidly metabolized to psilocin, which is a potent agonist at serotonin 5-$HT_{1A/2A/2C}$ receptors, with 5-HT_{2A} receptor activation directly correlated with human hallucinogenic activity.[16] Psilocybin was studied during the 1960s to establish its psychopharmacological profile; it was found to be active orally at around 10 mg, with stronger effects at higher doses, and to have a 4- to 6-hour duration of experience. Psychological effects were similar to those of ly-

sergic acid diethylamide (LSD), with psilocybin considered to be more strongly visual, less emotionally intense, more euphoric, and with fewer panic reactions and less chance of paranoia than LSD.[17,18]

Recent clinical examinations of psilocybin have indicated that it is not hazardous to physical health.[19] Positron emission tomographic studies demonstrated that psilocybin produces a global increase in cerebral metabolic rate of glucose, most markedly in the frontomedial and frontolateral cortex, anterior cingulate, and temporomedial cortex. These changes were correlated with measures of psychological state and consistent with potential neurobiological substrates of major mental illnesses.[20]

In one recent study, 36 healthy volunteers received a high dose (30 mg/70 kg) of psilocybin with no sustained deleterious physiological or psychological effects. The investigators corroborated previous findings that psilocybin could reliably catalyze mystical experiences leading to significant and lasting improvements in quality of life.[21] In another study, the effects of psilocybin were examined in patients with severe, refractory obsessive-compulsive disorder. Researchers concluded that psilocybin is safe and well tolerated in subjects with obsessive-compulsive disorder and may be associated with "robust acute reductions" in core obsessive-compulsive disorder symptoms, although there was no clear dose-response relationship.[22]

During the first wave of hallucinogen research from the 1950s through the early 1970s, investigators who administered hallucinogens to patients with end-stage cancers reported results that included improved mood and reduced anxiety, even in those with profound psychological demoralization.[23-26] The present study is the first in more than 35 years to explore the potential utility of a psilocybin treatment model for patients with reactive anxiety associated with advanced-stage cancer.[27]

METHODS

Twelve subjects with advanced-stage cancer and a *DSM-IV*[28] diagnosis of acute stress disorder, generalized anxiety disorder, anxiety disorder due to cancer, or adjustment disorder with anxiety were recruited into a within-subject, double-blind, placebo-controlled study to examine the safety and efficacy of psilocybin in the treatment of psychological distress associated with the existential crisis of terminal disease. Participants were recruited through Internet postings, flyer distribution, presentations at local hospitals and wellness centers, oncologist referrals, and study registration on clinicaltrials.gov and by contacting local patient support agencies and health care providers. Medical and psychiatric screening including brain magnetic resonance imaging, communication with treating oncologists, formal psychiatric diagnostic interviews, and informed consent were required for enrollment into the study. Subjects were not paid for their participation. The institutional review board of the Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, California, approved the protocol and monitored the study.

Of the 12 subjects, 11 were women. Subjects' ages ranged from 36 to 58 years. Primary cancers included breast cancer in 4 subjects, colon cancer in 3, ovarian cancer in 2, peritoneal cancer in 1, salivary gland cancer in 1, and multiple myeloma in 1. All subjects were in advanced stages of their illness. The duration of their primary cancers ranged from 2 months to 18 years. Eight subjects completed the 6-month follow-up assessment, 11 completed at least the first 4 months of assessment, and all 12 completed at least the first 3 months of follow-up. Two subjects died of their cancer during the follow-up period, and 2 others became too ill to continue participating. The study was conducted from June 2004 to May 2008. By the time of submission of this report in 2010, 10 of the 12 subjects had died.

Exclusion criteria included central nervous system involvement of the cancer, severe cardiovascular illness, untreated hypertension, abnormal hepatic or renal function, diabetes, lifetime history of schizophrenia, bipolar disease, other psychotic illness, and anxiety or affective disorders within 1 year prior to the onset of cancer. Medication contraindications included active cancer chemotherapy, antiseizure medications, insulin and oral hypoglycemics, and psychotropic medications in the previous 2 weeks. Subjects also were asked to refrain from taking any medications the day of and the day after the experimental treatment sessions, except for prescription or over-the-counter nonnarcotic pain medications at any time and narcotic pain medications up to 8 hours before and 6 hours after administration of the experimental medicine.

Four subjects had no prior hallucinogen experience. Of the remaining 8, 4 had hallucinogen experience more than 30 years ago. Two had their last experience more than 5 years ago, and the other 2 had taken a hallucinogen within the year prior to their participation in the study. Hallucinogens taken included LSD (7 subjects), hallucinogenic mushrooms (5 subjects), peyote (2 subjects), and ayahuasca (2 subjects).

Subjects met with study staff to review the purpose and intention of participation in the study, the treatment goals, the structure of the experimental treatment sessions, and critical issues to be examined during the course of the treatments. Subjects were informed of the range of emotional reaction that might be experienced while under the influence of psilocybin, including challenging psychological issues that might arise, and were informed that the purpose of the investigation was to determine whether psilocybin could ameliorate the anxiety associated with their advanced-stage cancer. Additional goals of these meetings included establishing a comfortable level of rapport and trust between the patient and research personnel, reviewing significant life issues in the patient's history, and the nature and status of present relationships and concerns.

All experimental sessions took place in a hospital clinical research unit in a room decorated with fabric wall hangings and fresh flowers to provide a pleasing and comfortable environment. Subjects were admitted on the afternoon of the day prior to treatment. A Holter cardiac monitor was attached for 24 hours beginning at admission. Following medical and nursing evaluations, the treatment team met with the subject to review the procedure for the treatment session (described later), confirm the subject's personal intentions, and answer any additional questions. Subjects spent the night in the room on the research unit and were provided dinner and a light breakfast before 06:30 hours. On the morning of treatment, the therapeutic team met with the subject to administer presession instruments, attend to patient comfort, and review treatment procedures for the session one final time.

Each subject acted as his or her own control and was provided 2 experimental treatment sessions spaced several weeks apart. They were informed that they would receive active psilocybin (0.2 mg/kg) on one occasion and the placebo, niacin (250 mg), on the other occasion. Psilocybin and placebo were administered in clear 00 capsules with corn starch and swallowed with 100 mL of water. A niacin placebo was chosen because it often induces a mild physiological reaction (eg, flush-

ing) without altering the psychological state. The order in which subjects received the 2 different treatments was randomized and known only by the research pharmacist. Treatment team personnel remained at the bedside with the subject for the entire 6-hour session.

Psilocybin or placebo was administered at 10:00 hours. The subject was encouraged to lie in bed wearing eye shades during the first few hours as well as to put on headphones to listen to preselected music. Subjects were allowed to remain undisturbed until each hour point, when treatment staff checked to inquire how they were doing. Contact was generally brief; subjects had been advised that there would be ample opportunity after the session and in subsequent days, weeks, and months to discuss the content of the experience. During hourly check-ins, heart rate (HR) and blood pressure (BP) measurements also were taken. Noncaffeinated clear liquids or juices were permitted.

At the conclusion of the 6-hour session, subjects discussed the subjective aesthetic, cognitive, affective, and psychospiritual experiences they had during the session and completed rating instruments. Various self-report inventories and questionnaires were administered from 2 weeks prior to the first treatment session to up to 6 months after the second. Treatment team personnel maintained contact with subjects for the entire 6-month follow-up period, including regularly scheduled monthly telephone calls to update data on adverse events, concomitant medications, and evolving medical and psychological status.

ASSESSMENT MEASURES

Subjects' BP and HR were measured 30 minutes before drug ingestion, immediately before drug administration, and at hourly intervals for the next 6 hours. Temperature was measured just prior to drug administration and 6 hours later at the conclusion of the session.

The following psychological measures were administered the day before each of the experimental sessions: the Beck Depression Inventory (BDI), Profile of Mood States (POMS), and State-Trait Anxiety Inventory (STAI). The POMS, STAI, 5-Dimension Altered States of Consciousness profile (5D-ASC), and Brief Psychiatric Rating Scale were administered at the conclusion of the experimental sessions. The day after the session, the BDI, POMS, and STAI were readministered. Finally, the BDI, POMS, and STAI were administered again 2 weeks after each session and at monthly intervals for 6 months after the final session.

INSTRUMENTS

Beck Depression Inventory

The BDI consists of a series of questions developed to measure the intensity, severity, and depth of depression.[29]

Profile of Mood States

The POMS describes feelings individuals have, with the subject indicating his or her mood during the past week, including the present day. The POMS Brief, used for this study, is a shorter version of the original POMS Standard.[30] Subjects were instructed to fill out the POMS and BDI in reference to their feelings during the past week.

State-Trait Anxiety Inventory

The STAI Form Y is a widely used self-report instrument for assessing anxiety in adults. It includes separate measures of state and trait anxiety.[31] The STAI evaluates the essential qualities of feelings of apprehension, tension, nervousness, and worry. The STAI differentiates between the temporary condition of state anxiety and the more general and long-standing quality of trait anxiety. The STAI state anxiety subscale asks for feelings at the moment of filling out the questionnaire, and the STAI trait anxiety subscale asks subjects to indicate how they generally view themselves.

Brief Psychiatric Rating Scale

The Brief Psychiatric Rating Scale provides clinician assessment of the level of symptoms such as hostility, suspiciousness, hallucination, and grandiosity.[32]

5-Dimension Altered States of Consciousness Profile

The 5D-ASC rating scale measures alterations in mood, perception, experience of self in relation to environment, and thought disorder.[33] The ASC items are grouped into 5 subscales comprising several items, including the following: (1) *oceanic boundlessness*, measuring derealization and depersonalization accompanied by changes in affect ranging from elevated mood to euphoria; (2) *anxious ego dissolution*, measuring ego disintegration associated with loss of self-control, thought disorder, arousal, and anxiety; (3) *visionary restructuralization*, including hallucinations, pseudohallucinations, synesthesia, changed meaning of perceptions, and facilitated recollection and imagination; (4) *auditory alterations*, with acoustic alterations and alterations of auditory experiences; and (5) *reduction of vigilance*, associated with drowsiness, reduced alertness, and related impairment of cognition. Subjects filled out the 5D-ASC at the conclusion of the session.

DATA ANALYSIS

Raw BDI, POMS, and STAI data were analyzed using 2-way analysis of variance (ANOVA) with drug as the within-subject factor and day as a repeated measure. When the 2-way ANOVA detected significant main effects of drug or interactions between day and drug, post hoc pairwise comparisons were performed by 1-way ANOVA for each day. The 5D-ASC data were analyzed using 1-way ANOVA with drug as a within-subject factor. Item clusters comprising the oceanic boundlessness, anxious ego dissolution, and visionary restructuralization dimensions also were analyzed using 1-way ANOVA.[34] The Brief Psychiatric Rating Scale data were analyzed using 1-way ANOVA with drug as a within-subject factor. The HR and BP data were analyzed using 2-way ANOVA with drug as a within-subject factor and time as a repeated measure. When the 2-way ANOVA detected significant main effects of drug or interactions between time and drug, pairwise post hoc comparisons were performed by 1-way ANOVA at each time. For the measures listed earlier, significance was demonstrated by surpassing an α level of .05. Paired *t* tests were used to assess whether niacin placebo and psilocybin produced effects on HR and BP compared with the predrug time, and significance was demonstrated for these multiple comparisons by surpassing an α level of .025. For the BDI, POMS, and STAI, data from each of the 6 follow-up times were compared with the baseline value obtained on the day before the first treatment session, using *t* tests. For the follow-up data, significance was demonstrated by surpassing an α level of .05.

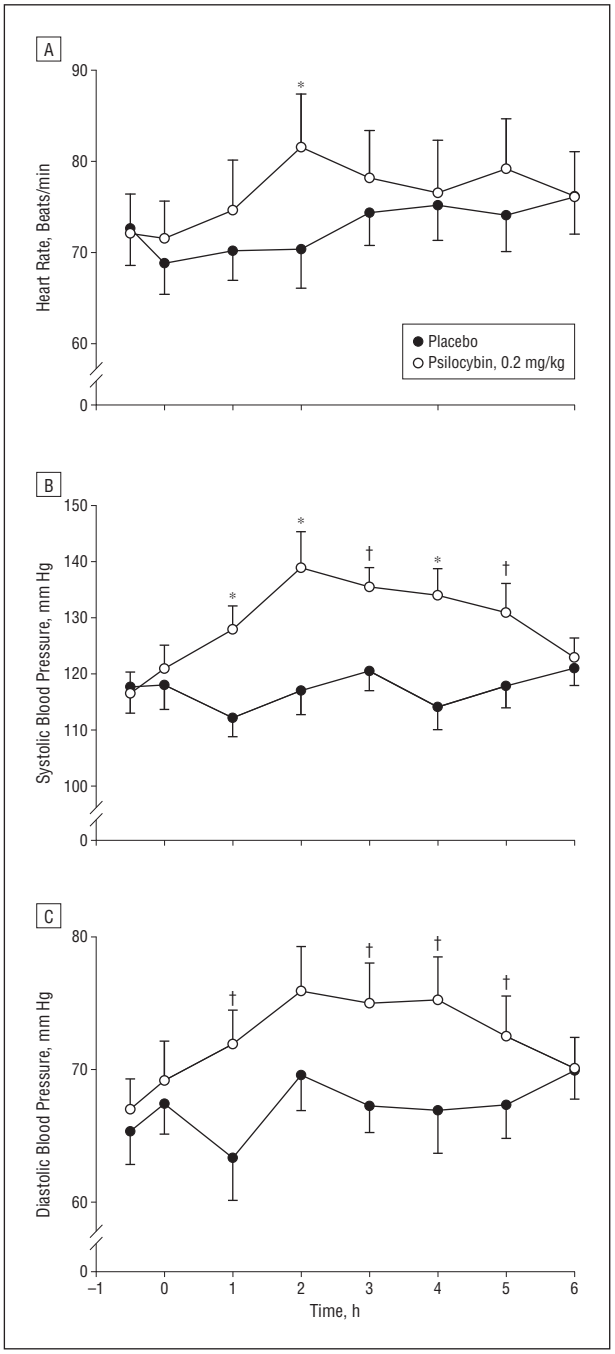

Figure 1. Effect of psilocybin or niacin placebo on mean (SEM) heart rate (A), systolic blood pressure (B), and diastolic blood pressure (C). Psilocybin or niacin placebo was administered at 0 hours.*$P<.01$, †$P<.05$ for psilocybin vs niacin placebo control (1-way analyses of variance were used to compare niacin and psilocybin effects at individual times).

RESULTS

CARDIOVASCULAR FUNCTION

The administration of psilocybin at a dose of 0.2 mg/kg induced a mild but statistically significant elevation of HR (psilocybin × time interaction: $F_{7,70}=2.40$, $P=.03$), systolic BP ($F_{1,11}=25.39$, $P<.001$), and diastolic BP ($F_{1,11}=5.94$, $P=.03$) when compared with niacin placebo. Elevation of HR peaked 2 hours after psilocybin administration, with a mean (SEM) peak effect of 81.5 (5.8) beats/min, which was statistically significant ($F_{1,11}=11.31$, $P<.007$) compared with 70.4 (4.3) beats/min during placebo sessions (**Figure 1**A).

Blood pressure also peaked at the 2-hour point, with mean (SEM) peak systolic BP during psilocybin sessions measuring 138.9 (6.4) mm Hg (compared with 117.0 [4.3] mm Hg during niacin placebo sessions) (Figure 1B) and mean (SEM) peak diastolic BP of 75.9 (3.4) mm Hg during psilocybin sessions (compared with 69.6 [2.7] mm Hg during niacin placebo sessions) (Figure 1C). Holter monitor recordings during the psilocybin sessions showed no sustained tachyarrhythmias or heart block and were consistent with findings during active placebo sessions. Compared with the predrug time, niacin modestly depressed diastolic BP 1 hour after administration (Figure 1C) with a rebound over the next hour but had no effect at other times.

PSYCHOLOGICAL MEASURES

The 5D-ASC demonstrated marked subjective differences between the psilocybin and placebo experiences. Psilocybin particularly affected the oceanic boundlessness ($F_{1,11}=33.12$, $P<.001$) and visionary restructuralization ($F_{1,11}=18.95$, $P=.001$) dimensions (**Figure 2**A). Psilocybin had smaller but significant effects on anxious ego dissolution ($F_{1,11}=4.91$, $P=.049$) and auditory alterations ($F_{1,11}=5.93$, $P=.03$). The item clusters with marked differences between the subjective states produced by psilocybin and niacin included a significant increase ($P<.05$) in psilocybin-invoked states of positive derealization, positive depersonalization, altered sense of time, positive mood, manialike experiences, elementary hallucinations, visual pseudohallucinations, synesthesia, changed meaning of percepts, facilitated recollection, and facilitated imagination. Subscales with no appreciable differences between intrasubjective states induced by the 2 treatments included anxious derealization, thought disorder, delusion, fear of loss of thought control, and fear of loss of body control (Figure 2B).

For the BDI, there was an overall interaction of psilocybin and day that approached but did not attain statistical significance ($F_{1,11}=3.75$, $P=.08$). There was no appreciable change from 1 day prior to placebo administration to 2 weeks after experimental treatment, whereas a trend was observed after psilocybin administration, from a mean (SEM) score of 16.1 (3.6) one day before treatment to 10.0 (2.7) two weeks after treatment (**Figure 3**A). As shown in Figure 3B, BDI scores dropped by almost 30% from the first session to 1 month after the second treatment session ($t_{11}=-2.17$, $P=.05$), a difference that was sustained and became significant at the 6-month follow-up point ($t_7=2.71$, $P=.03$).

The POMS similarly revealed a trend for reduced adverse mood tone from 1 day before treatment with psilocybin to 2 weeks later, a difference that was not seen after placebo (drug × time interaction: $F_{3,33}=2.71$, $P=.06$) (**Figure 4**A). Paired post hoc tests revealed that mean (SEM) POMS scores were elevated ($F_{1,11}=7.48$, $P=.02$) 1 day before psilocybin treatment (11.3 [3.1]) compared with 1 day before placebo (4.5 [2.0]) and demonstrated

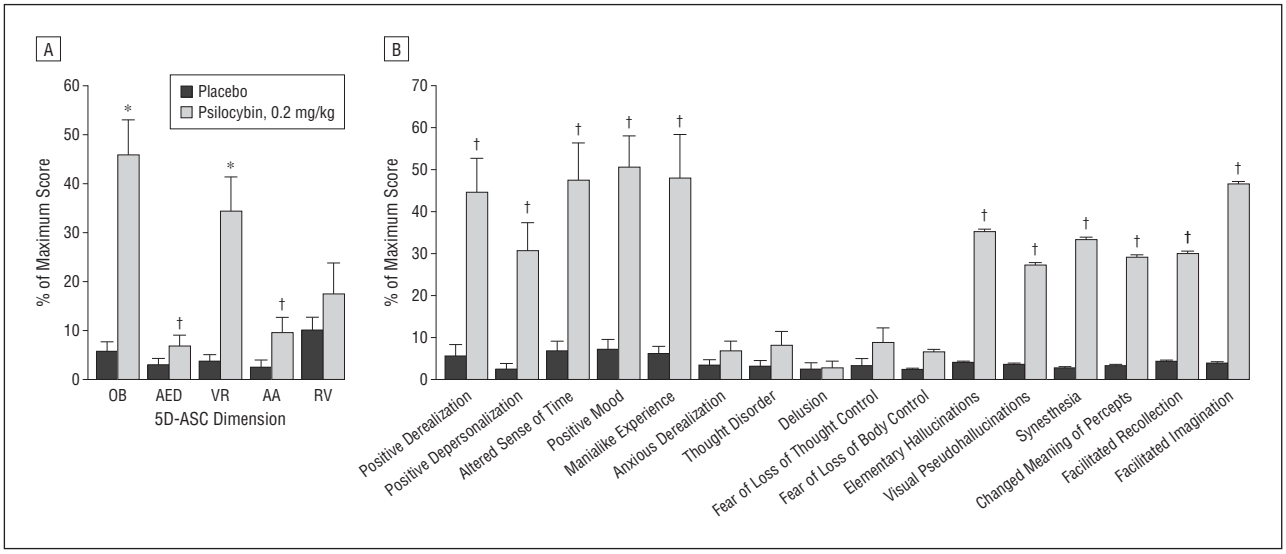

Figure 2. Subjective effects of psilocybin as measured by the 5-Dimension Altered States of Consciousness profile (5D-ASC). A, Five main 5D-ASC dimensions are shown: oceanic boundlessness (OB), anxious ego dissolution (AED), visionary restructuralization (VR), auditory alterations (AA), and reduced vigilance (RV). B, Item clusters comprising the OB, AED, and VR dimensions are shown. Values are the mean (SEM) percentages of the total possible score. *$P<.01$, †$P<.05$ for psilocybin vs niacin placebo control (1-way analyses of variance were used to compare niacin and psilocybin effects on individual 5D-ASC dimensions and 5D-ASC item clusters).

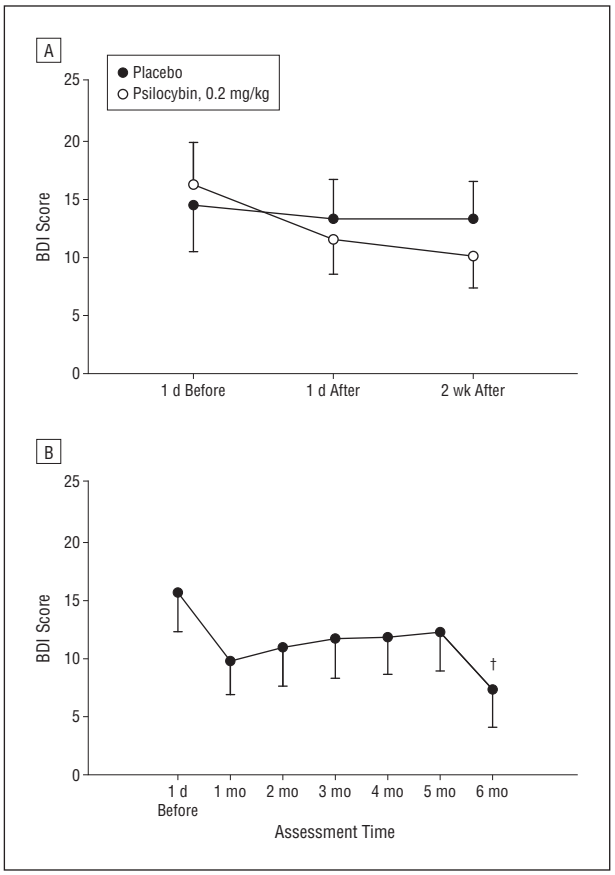

Figure 3. Beck Depression Inventory (BDI) scores. A, Mean (SEM) BDI scores 1 day before, 1 day after, and 2 weeks after administration of psilocybin or niacin placebo are shown. B, Six months of mean (SEM) BDI follow-up data are shown. The BDI was administered at monthly intervals for 6 months after 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). †$P<.05$ 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).

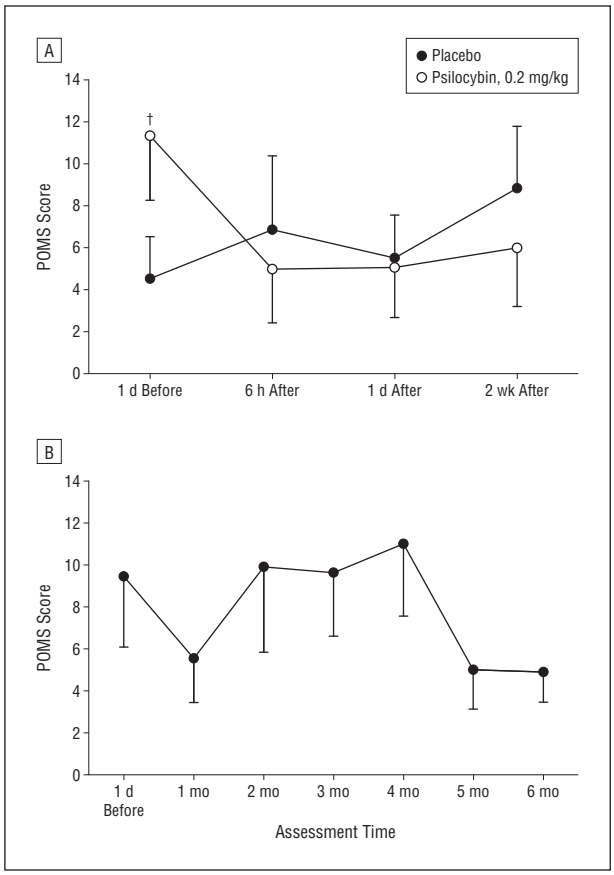

Figure 4. Profile of Mood States (POMS) scores. A, Mean (SEM) POMS scores 1 day before, 6 hours after, 1 day after, and 2 weeks after administration of psilocybin or niacin placebo are shown. B, Six months of mean (SEM) POMS follow-up data are shown. The POMS was administered at monthly intervals for 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). †$P<.05$ for psilocybin vs niacin placebo control (1-way analyses of variance were used to compare niacin and placebo effects at individual times).

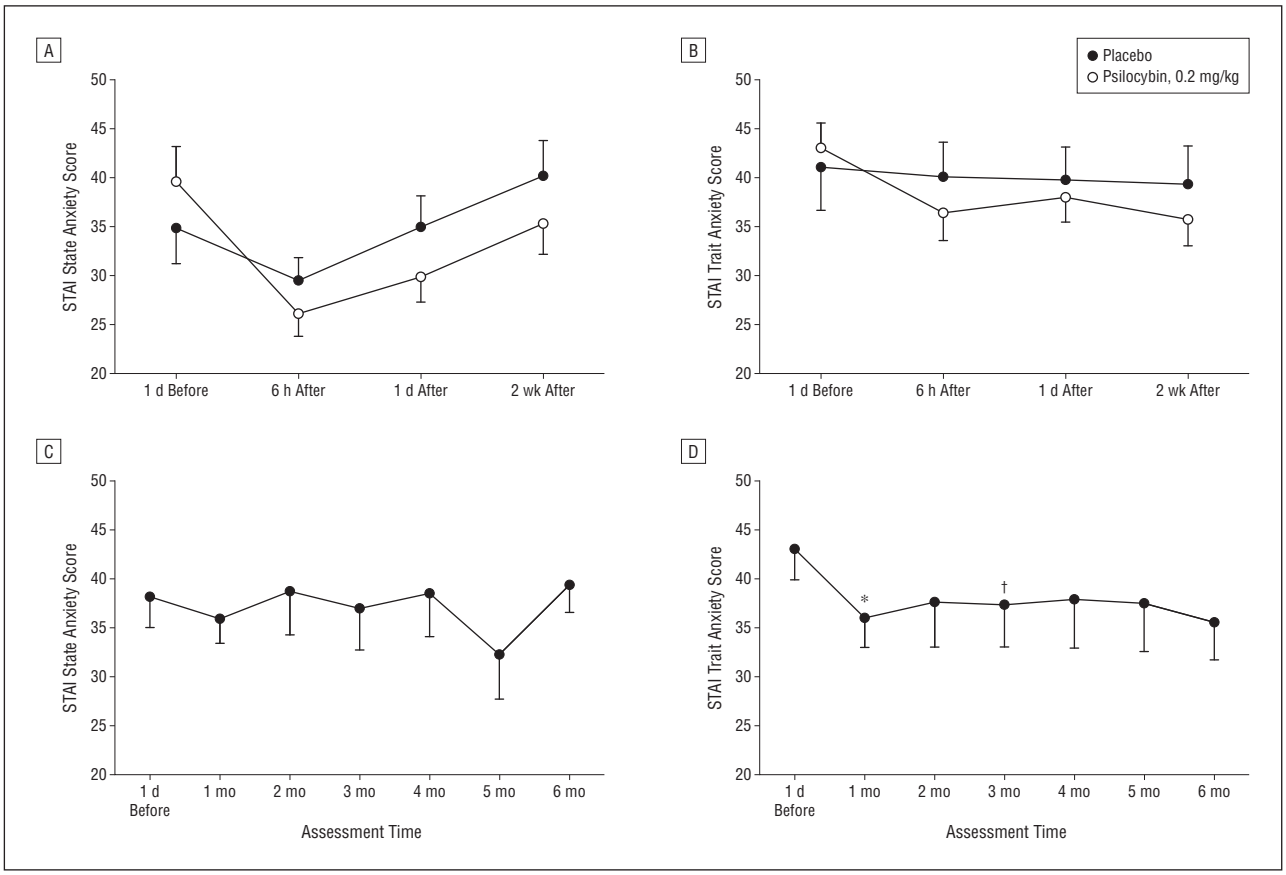

Figure 5. Mean (SEM) State-Trait Anxiety Index (STAI) state anxiety scores (A) and trait anxiety scores (B) 1 day before, 6 hours after, 1 day after, and 2 weeks after administration of psilocybin or niacin placebo are shown. Six months of mean (SEM) STAI state anxiety follow-up data (C) and trait anxiety 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).

that this difference disappeared 6 hours after psilocybin administration. Improvement of mood, indicated by reduced POMS scores, was observed in 11 subjects after administration of psilocybin. The elevation of POMS scores 1 day before psilocybin treatment occurred regardless of whether the subjects were treated with placebo or psilocybin first (ie, there was no interaction between treatment order and drug). As shown in Figure 4B, POMS scores were not altered during the 6 months of follow-up compared with the day before the first treatment session.

The STAI revealed no significant changes from 1 day before to 2 weeks after treatment, although a substantial but nonsignificant decrease was evident for the state anxiety subscale 6 hours after psilocybin administration, which was not observed after placebo (**Figure 5**A and C). Although minimal change was observed in the STAI state anxiety score for follow-up data, a sustained decrease in STAI trait anxiety was observed for the entire 6-month follow-up, reaching significance at the 1-month ($t_{11}=4.36$, $P=.001$) and 3-month ($t_{10}=2.55$, $P=.03$) points after the second treatment session (Figure 5B and D).

The Brief Psychiatric Rating Scale at the end of the experimental session revealed no appreciable difference between psilocybin and placebo administration.

COMMENT

The initial goals of this research project were to establish feasibility and safety for a hallucinogen treatment model in patients with advanced-stage cancer and anxiety. Following discussion with federal and state regulatory agencies as well as hospital institutional review board and research committees, a modest 0.2-mg/kg psilocybin dose was chosen. Although not comparable to higher doses of hallucinogens administered in the past to severely ill patients, the dose used here was still believed capable of inducing an alteration of consciousness with potential therapeutic benefit while optimizing patient safety. Determining safe parameters with this novel treatment paradigm is critical to establishing a strong foundation for this field of study that would allow for future investigations.

Consistent with previous research, we found no untoward cardiovascular sequelae in our subject population.[19] Minor HR and BP elevations after psilocybin administration were evidence only of a mild sympathomimetic effect. Holter monitoring did not identify increased cardiac arrhythmias in comparison with niacin placebo, even in subjects who presented with some baseline cardiac arrhythmia. Niacin may acutely lower BP through vasodi-

lation[35] but had minimal effects on BP and HR in our subjects, except for a reduction in diastolic BP that was noted 1 hour after administration of niacin. This transient effect may have contributed to our detection of a significant psilocybin effect at that time but cannot explain the significant effects of psilocybin over the subsequent intervals because the initial niacin-induced reduction of diastolic BP did not persist. We also observed no adverse psychological effects from the treatment. All subjects tolerated the treatment sessions well, with no indication of severe anxiety or a "bad trip." The fact that psilocybin produced only modest effects on the anxious ego dissolution scale of the 5D-ASC confirmed this conclusion.

When hallucinogens were administered to patients with terminal cancer in the 1960s and early 1970s, the occurrence of a profound psychospiritual experience was correlated with therapeutic outcome.[10,12] Such transcendent states of consciousness are usually associated with higher doses of hallucinogens, so our expectation of demonstrating efficacy was limited.[21] Common themes reported by subjects included examining how their illness had impacted their lives, relationships with family and close friends, and sense of ontological security. In addition, subjects reported powerful empathic cathexis to close friends and family members and examined how they wished to address their limited life expectancy. In monthly follow-up discussions, subjects reflected on insights and new perspectives gained during their psilocybin treatment. However, the frequency of these reports was not quantified.

Although past researchers reported more pronounced therapeutic effects with a higher-dose model, even the lower dose of psilocybin used in the current study gave some indication of therapeutic benefit in quantitative psychological evaluations. In particular, we found that the STAI trait anxiety subscale demonstrated a sustained reduction in anxiety that reached significance at the 1- and 3-month points after treatment. This reduction might reflect a reduced level of stress and anxiety over time. Although the state anxiety on the STAI showed a modest elevation at 6 months, the change was not statistically significant and might have resulted from the deteriorating medical status of most subjects over time.

Mood also improved for 2 weeks after treatment with psilocybin, with sustained improvement on the BDI reaching significance at the 6-month follow-up point. The POMS scores also reflected improved mood 2 weeks after receiving psilocybin. Although not statistically significant, there was a trend toward positive outcome. With a larger cohort of subjects and use of a higher dose of psilocybin, it seems possible that significant results would be obtained on these measures.

Compared with placebo sessions, POMS scores were elevated in subjects immediately prior to psilocybin administration. The reasons for this difference in POMS scores 1 day before administration are not entirely clear. Subject expectations were unlikely to have played a role in the elevation of the POMS scores on the day before treatment because the elevation occurred regardless of treatment order. The most likely explanation for the elevation of POMS scores prior to treatment with psilocybin may be that subject randomization was not complete with regard to this instrument. Nonetheless, POMS scores declined after administration of psilocybin in 11 of 12 subjects, suggesting that psilocybin produces mood-elevating effects that persist after the acute effects of the drug.

Another focus of the study was the effect of a 0.2-mg/kg psilocybin dose on somatic symptoms, particularly pain perception. In contrast to previous investigations, we did not find robust reductions in pain perception or lessened need for narcotic pain medication. In the 2 weeks following experimental treatment sessions, several subjects reported lessened pain, whereas others did not. There was no apparent difference between subjects treated with psilocybin and those treated with placebo (data not shown). Although this modest dose of psilocybin was not observed to impact pain, given the impressive reports of earlier researchers,[6] this measure would certainly be indicated for study with higher doses.

Although we used a within-subject, double-blind, placebo-controlled design, the drug order was almost always apparent to subjects and investigators whether the treatment was psilocybin or placebo. In fact, one consistent subject critique of the study was that the placebo sessions were perceived as far less worthwhile than those with psilocybin. Many of the subjects suggested that future protocols provide the opportunity for a second psilocybin session several weeks after the first. The general consensus among subjects was that a follow-up experience with psilocybin would reinforce and extend the perceived therapeutic effects of the initial session.

Future studies also will need to address the issue of controlling for a placebo effect that might otherwise be attributed to the active treatment. Given the subjects' grave prognosis and limited life expectancy, we decided to provide all subjects with an opportunity to experience the experimental medicine and to serve as their own control. Although we believed that to be the ethical course to take, given the life circumstances subjects were encountering, the protocol design contains some inherent limitations. A better experimental design might incorporate an independent control group, receiving only either placebo treatment or a conventional psychopharmacological intervention. Although there is no question that the extensive attention paid to the subjects influenced outcomes, the unique qualities of the psilocybin experience in facilitating strong therapeutic bonds and ameliorating underlying psychological demoralization are important factors worthy of further exploration.

Another limitation of this study was variability in the extent of contact with subjects after treatment. A minimum contact of 1 hour monthly was established, but variability in additional ad hoc communication depended on the needs and wishes of the subjects, some of whom were near death compared with others who were more functional.

Despite the limitations, this study demonstrates that the careful and controlled use of psilocybin may provide an alternative model for the treatment of conditions that are often minimally responsive to conventional therapies, including the profound existential anxiety and despair that often accompany advanced-stage cancers. A recent review from the psilocybin research group at Johns Hopkins University describes the critical components necessary for ensuring subject safety in hallucinogen research.[36]

Taking into account these essential provisions for optimizing safety as well as adhering to strict ethical standards of conduct for treatment facilitators, the results provided herein indicate the safety and promise of continued investigations into the range of medical effects of hallucinogenic compounds such as psilocybin.

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REFERENCES

1. Breitbart W, Gibson C, Poppito SR, Berg A. Psychotherapeutic interventions at the end of life: a focus on meaning and spirituality. *Can J Psychiatry*. 2004;49(6):366-372.
2. Breitbart W, Rosenfeld B, Pessin H, Kaim M, Funesti-Esch J, Galietta M, Nelson CJ, Brescia R. Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. *JAMA*. 2000;284(22):2907-2911.
3. Chochinov HM. Psychiatry and terminal illness. *Can J Psychiatry*. 2000;45(2):143-150.
4. Rousseau P. Spirituality and the dying patient. *J Clin Oncol*. 2000;18(9):2000-2002.
5. Kast EC. The measurement of pain, a new approach to an old problem. *J New Drugs*. 1962;2:344-351.
6. Kast EC. Pain and LSD-25: a theory of attenuation of anticipation. In: Solomon D, ed. *LSD: The Consciousness-Expanding Drug*. New York, NY: GP Putnam; 1966:239-254.
7. Kast EC. LSD and the dying patient. *Chic Med Sch Q*. 1966;26(2):80-87.
8. Kast EC. A concept of death. In: Aronson B, Osmond H, eds. *Psychedelics: The Uses and Implications of Hallucinogenic Drugs*. Garden City, NY: Anchor; 1970:266-381.
9. Kast EC, Collins VJ. Study of lysergic acid diethylamide as an analgesic agent. *Anesth Analg*. 1964;43:285-291.
10. Pahnke WN. The psychedelic mystical experience in the human encounter with death. *Harv Theol Rev*. 1969;62(1):1-21.
11. Grof S. *LSD Psychotherapy*. Pomona, CA: Hunter House; 1980.
12. Grof S, Goodman LE, Richards WA, Kurland AA. LSD-assisted psychotherapy in patients with terminal cancer. *Int Pharmacopsychiatry*. 1973;8(3):129-144.
13. Richards WA, Grof S, Goodman LE, Kurland AA. LSD-assisted psychotherapy and the human encounter with death. *J Transpers Psychol*. 1972;4(2):121-150.
14. Fisher G. Death, identity and creativity. *Voices: Art Sci Psychother*. 1969;5:36-39.
15. Fisher G. Psychotherapy for the dying: principles and illustrative cases with special reference to the use of LSD. *Omega*. 1970;1(1):3-15.
16. Presti D, Nichols D. Biochemistry and neuropharmacology of psilocybin mushrooms. In: Metzner R, ed. *Teonanacatl: Sacred Mushroom of Vision*. El Verano, CA: Four Trees; 2004:89-108.
17. Passie T, Seifert J, Schneider U, Emrich HM. The pharmacology of psilocybin. *Addict Biol*. 2002;7(4):357-364.
18. Passie T. A history of the use of psilocybin in psychotherapy. In: Metzner R, ed. *Teonanacatl: Sacred Mushroom of Vision*. El Verano, CA: Four Trees; 2004:109-134.
19. Hasler F, Grimberg U, Benz MA, Huber T, Vollenweider FX. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. *Psychopharmacology (Berl)*. 2004;172(2):145-156.
20. Vollenweider FX, Leenders KL, Scharfetter C, Maguire P, Stadelmann O, Angst J. Positron emission tomography and fluorodeoxyglucose studies of metabolic hyperfrontality and psychopathology in the psilocybin model of psychosis. *Neuropsychopharmacology*. 1997;16(5):357-372.
21. Griffiths RR, Richards WA, McCann U, Jesse R. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology (Berl)*. 2006;187(3):268-283, discussion 284-292.
22. Moreno FA, Wiegand CB, Taitano EK, Delgado PL. Safety, tolerability, and efficacy of psilocybin in 9 patients with obsessive-compulsive disorder. *J Clin Psychiatry*. 2006;67(11):1735-1740.
23. Grinspoon L, Bakalar JB. *Psychedelic Drugs Reconsidered*. New York, NY: Basic Books; 1979.
24. Grob CS. Psychiatric research with hallucinogens: what have we learned? *Heffter Rev Psychedelic Res*. 1998;1:8-20.
25. Grob CS, ed. *Hallucinogens: A Reader*. New York, NY: Tarcher/Putnam; 2002.
26. Walsh R, Grob CS, eds. *Higher Wisdom: Eminent Elders Explore the Continuing Impact of Psychedelics*. Albany: State University of New York; 2005.
27. Grob CS. The use of psilocybin in patients with advanced cancer and existential anxiety. In: Winkelman MJ, Roberts TB, eds. *Psychedelic Medicine: New Evidence for Hallucinogenic Substances as Treatment*. Westport, CT: Praeger; 2007:205-216.
28. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed, text revision. Washington, DC: American Psychiatric Association; 2000.
29. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4(6):561-571.
30. Cella DF, Jacobsen PB, Orav EJ, Holland JC, Silberfarb PM, Rafla S. A brief POMS measure of distress for cancer patients. *J Chronic Dis*. 1987;40(10):939-942.
31. Spielberger CD, Gorsuch RL, Lushene R, Vagg PR, Jacobs GA. *State-Trait Anxiety Inventory*. Menlo Park, CA: Mind Garden; 1970.
32. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10:799-812.
33. Dittrich A, Lamparter D, Maurer M. *5D-ABZ: Fragebogen zur Erfassung Aussergewöhnlicher Bewusstseinszustände: Eine kurze Einführung*. Zürich, Switzerland: PSIN Plus; 1999.
34. Vollenweider FX, Csomor PA, Knappe B, Geyer MA, Quednow BB. The effects of the preferential 5-HT2A agonist psilocybin on prepulse inhibition of startle in healthy human volunteers depend on interstimulus interval. *Neuropsychopharmacology*. 2007;32(9):1876-1887.
35. Bays HE, Rader DJ. Does nicotinic acid (niacin) lower blood pressure? *Int J Clin Pract*. 2009;63(1):151-159.
36. Johnson MW, Richards WA, Griffiths RR. Human hallucinogen research: guidelines for safety. *J Psychopharmacol*. 2008;22(6):603-620.

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

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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. Instructions to participants and staff minimized expectancy effects. Participants, staff, and community observers rated participant moods, attitudes, and behaviors throughout the study. High-dose psilocybin produced large decreases in clinician- and self-rated measures of depressed mood and anxiety, along with increases in quality of life, life meaning, and optimism, and decreases in death anxiety. At 6-month follow-up, these changes were sustained, with about 80% of participants continuing to show clinically significant decreases in depressed mood and anxiety. Participants attributed improvements in attitudes about life/self, mood, relationships, and spirituality to the high-dose experience, with >80% endorsing moderately or greater increased well-being/life satisfaction. Community observer ratings showed corresponding changes. Mystical-type psilocybin experience on session day mediated the effect of psilocybin dose on therapeutic outcomes.

Trial Registration

ClinicalTrials.gov identifier: NCT00465595

Keywords

Psilocybin, hallucinogen, cancer, anxiety, depression, symptom remission, mystical experience

Introduction

Cancer patients often develop a chronic, clinically significant syndrome of psychosocial distress having depressed mood, anxiety, and reduced quality of life as core features, with up to 40% of cancer patients meeting criteria for a mood disorder (Holland et al., 2013; Mitchell et al., 2011). In cancer patients, depression and anxiety have been associated with decreased treatment adherence (Arrieta et al., 2013; Colleoni et al., 2000), prolonged hospitalization (Prieto et al., 2002), decreased quality of life (Arrieta et al., 2013; Skarstein et al., 2000), and increased suicidality (Shim and Park, 2012). Depression is an independent risk factor of early death in cancer patients (Arrieta et al., 2013; Pinquart and Duberstein, 2010). Antidepressants and, less frequently, benzodiazepines are used to treat depressed mood and anxiety in cancer patients, although evidence suggesting efficacy is limited and conflicting, and benzodiazepines are generally only recommended for short-term use because of side effects and withdrawal (Grassi et al., 2014; Ostuzzi et al., 2015; Walker et al., 2014). Although psychological approaches have shown only small to medium effects in treating emotional distress and quality of life, with low quality of reporting in many trials (Faller et al., 2013), there are several promising interventions utilizing existential orientations to psychotherapy (Breitbart et al., 2015; Spiegel, 2015).

The classic hallucinogens, which include psilocybin (psilocin) and (+)-lysergic acid diethylamide (LSD), are a structurally diverse group of compounds that are 5-HT_{2A} receptor agonists and produce a unique profile of changes in thoughts, perceptions, and emotions (Halberstadt, 2015; Nichols, 2016). Several unblinded studies in the 1960s and 70s suggested that such compounds might be effective in treating psychological distress in cancer patients (Grof et al., 1973; Kast, 1967; Richards et al., 1977); however, these studies did not include the comparison conditions that would be expected of modern psychopharmacology trials.

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Subsequently, human research with these compounds was halted for almost three decades because of safety and other concerns raised in response to widespread non-medical use in the 1960s. Recent resumption of clinical research with these compounds has established conditions for safe administration (Johnson et al., 2008; Studerus et al., 2011).

Two recent double-blind, placebo-controlled studies with the classic hallucinogens psilocybin (Grob et al., 2011) and LSD (Gasser et al., 2014) examined effects in 12 patients with life-threatening illness, including cancer. Both studies showed promising trends toward decreased psychological distress. Of most relevance to the present study with psilocybin, Grob and colleagues showed that a low-moderate dose of psilocybin (14 mg/70 kg) decreased a measure of trait anxiety at 1 and 3 months and depressed mood at 6-month follow-up. Also relevant, a recent open-label pilot study in 12 patients with treatment-resistant depression showed marked reductions in depressive symptoms 1 week and 3 months after administration of 10 and 25 mg of psilocybin in two sessions separated by 7 days (Carhart-Harris et al., 2016).

The present study provides the most rigorous evaluation to date of the efficacy of a classic hallucinogen for treatment of depressed mood and anxiety in psychologically distressed cancer patients. The study evaluated a range of clinically relevant measures using a double-blind cross-over design to compare a very low psilocybin dose (intended as a placebo) to a moderately high psilocybin dose in 51 patients under conditions that minimized expectancy effects.

Methods

Study participants

Participants with a potentially life-threatening cancer diagnosis and a DSM-IV diagnosis that included anxiety and/or mood symptoms were recruited through flyers, internet, and physician referral. Of 566 individuals who were screened by telephone, 56 were randomized. Figure 1 shows a CONSORT flow diagram. Table 1 shows demographics for the 51 participants who completed at least one session. The two randomized groups did not significantly differ demographically. All 51 participants had a potentially life-threatening cancer diagnosis, with 65% having recurrent or metastatic disease. Types of cancer included breast (13 participants), upper aerodigestive (7), gastrointestinal (4), genitourinary (18), hematologic malignancies (8), other (1). All had a DSM-IV diagnosis: chronic adjustment disorder with anxiety (11 participants), chronic adjustment disorder with mixed anxiety and depressed mood (11), dysthymic disorder (5), generalized anxiety disorder (GAD) (5), major depressive disorder (MDD) (14), or a dual diagnosis of GAD and MDD (4), or GAD and dysthymic disorder (1). Detailed inclusion/exclusion criteria are in the online Supplementary material. The Johns Hopkins IRB approved the study. Written informed consent was obtained from participants.

Study design and overview

A two-session, double-blind cross-over design compared the effects of a low versus high psilocybin dose on measures of depressed mood, anxiety, and quality of life, as well as measures of short-term and enduring changes in attitudes and behavior. Participants were randomly assigned to one of two groups. The Low-Dose-1st Group received the low dose of psilocybin on the first session and the high dose on the second session, whereas the High-Dose-1st Group received the high dose on the first session and the low dose on the second session. The duration of each participant's participation was approximately 9 months (mean 275 days). Psilocybin session 1 occurred, on average, approximately 1 month after study enrollment (mean 28 days), with session 2 occurring approximately 5 weeks later (mean 38 days). Data assessments occurred: (1) immediately after study enrollment (Baseline assessment); (2) on both session days (during and at the end of the session); (3) approximately 5 weeks (mean 37 days) after each session (Post-session 1 and Post-session 2 assessments); (4) approximately 6 months (mean 211 days) after Session 2 (6-month follow-up).

Interventions

Meetings with session monitors. After study enrollment and assessment of baseline measures, and before the first psilocybin session, each participant met with the two session monitors (staff who would be present during session days) on two or more occasions (mean of 3.0 occasions for a mean total of 7.9 hours). The day after each psilocybin session participants met with the session monitors (mean 1.2 hours). Participants met with monitors on two or more occasions between the first and second psilocybin session (mean of 2.7 occasions for a mean total of 3.4 hours) and on two or more occasions between the second session and 6-month follow-up (mean of 2.5 occasions for a mean total of 2.4 hours). Preparation meetings, the first meeting following each session, and the last meeting before the second session were always in person. For the 37 participants (73%) who did not reside within commuting distance of the research facility, 49% of the Post-session 1 meetings with monitors occurred via telephone or video calls.

A description of session monitor roles and the content and rationale for meetings between participants and monitors is provided elsewhere (Johnson et al., 2008). Briefly, preparation meetings before the first session, which included discussion of meaningful aspects of the participant's life, served to establish rapport and prepare the participant for the psilocybin sessions. During sessions, monitors were nondirective and supportive, and they encouraged participants to "trust, let go and be open" to the experience. Meetings after sessions generally focused on novel thoughts and feelings that arose during sessions. Session monitors were study staff originally trained by William Richards PhD, a clinical psychologist with extensive experience conducting studies with classic hallucinogens. Monitor education varied from college graduate to PhD. Formal clinical training varied from none to clinical psychologist. Monitors were selected as having significant human relations skills and self-described experience with altered states of consciousness induced by means such as meditation, yogic breathing, or relaxation techniques.

Psilocybin sessions. Drug sessions were conducted in an aesthetic living-room-like environment with two monitors present. Participants were instructed to consume a low-fat breakfast before coming to the research unit. A urine sample was taken to verify abstinence from common drugs of abuse (cocaine, benzodiazepines, and opioids including methadone). Participants who reported use of cannabis or dronabinol were instructed not

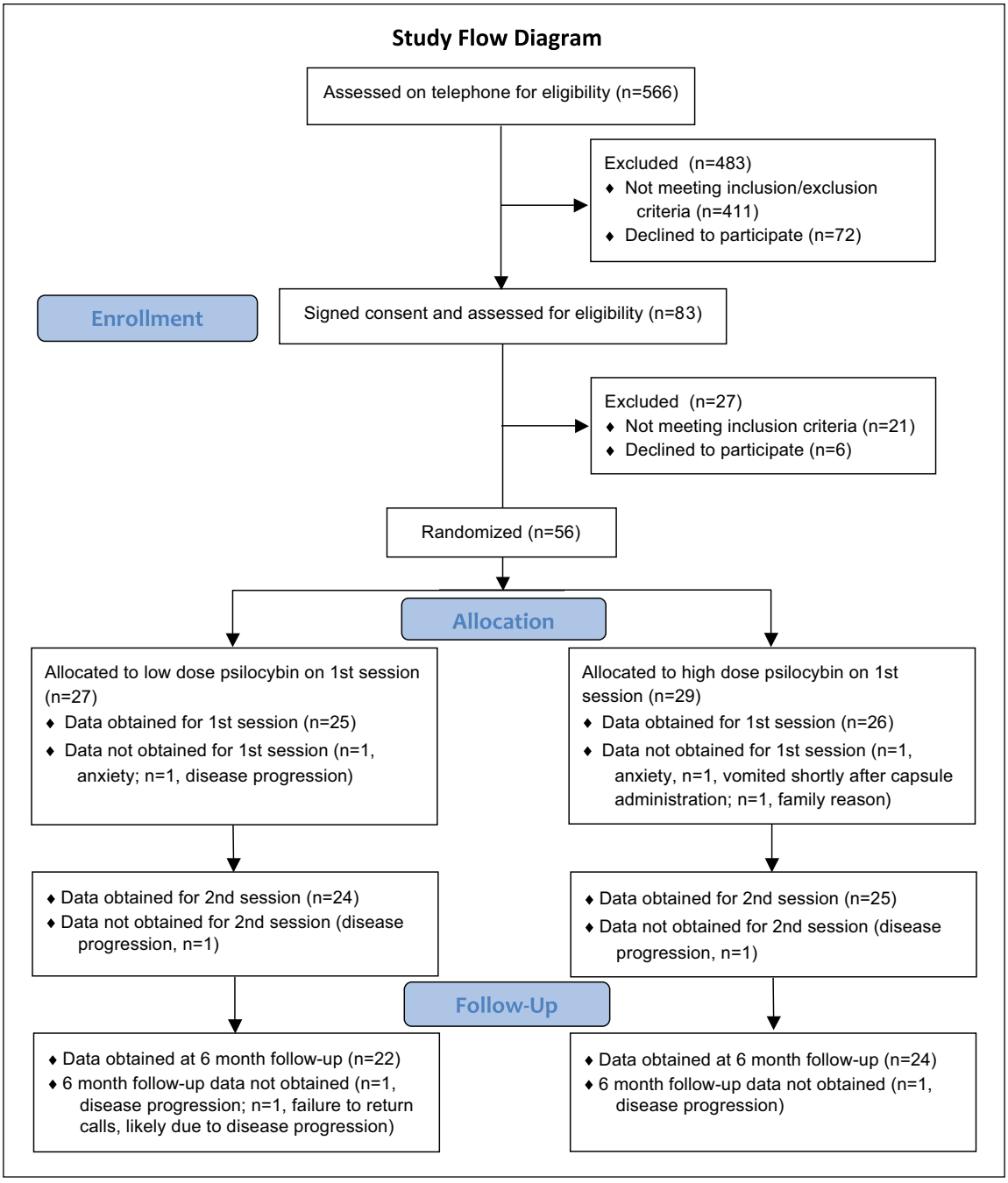

Figure 1. Flow diagram showing participation across the study.

to use for at least 24 h before sessions. Psilocybin doses were administered in identically appearing opaque, size 0 gelatin capsules, with lactose as the inactive capsule filler. For most of the time during the session, participants were encouraged to lie down on the couch, use an eye mask to block external visual distraction, and use headphones through which a music program was played. The same music program was played for all participants in both sessions. Participants were encouraged to focus their attention on their inner experiences throughout the session. Thus, there was no explicit instruction for participants to focus on their attitudes, ideas, or emotions related to their cancer. A more detailed description of the study room and procedures followed on session days is provided elsewhere (Griffiths et al., 2006; Johnson et al., 2008).

Instructions to participants and monitors to facilitate dose condition blinding and minimize expectancy effects. Expectancies, on part of both participants and monitors, are believed to play a large role in the qualitative effects of psilocybin-like drugs (Griffiths et al., 2006; Metzner et al., 1965). Although double-blind methods are usually used to protect against such effects, expectancy is likely to be significantly operative in a standard drug versus placebo design when the drug being evaluated produces highly discriminable effects and participants and staff

Table 1. Participant demographics for all participants and for both of the dose sequence groups separately+.

Measure	Low-Dose-1st (High-Dose-2nd) (*n*=25)	High-Dose-1st (Low-Dose-2nd) (*n*=26)	All Participants (*n*=51)
Gender (% female)	48%	50%	49%
Age in years (mean, SEM)	56.1 (2.3)	56.5 (1.8)	56.3 (1.4)
Race/Ethnicity			
White	92%	96%	94%
Black/African American	4%	4%	4%
Asian	4%	0%	2%
Education			
High school	4%	0%	2%
College	32%	58%	45%
Post-graduate	64%	42%	53%
Relationship status (married or living with partner)	72%	65%	69%
Lifetime use of hallucinogens			
Percent reporting any past use	56%	36%	45%
Years since last use (mean, SEM)	30.9 (3.2)	30.0 (4.5)	30.6 (2.6)
Recent use of cannabis or dronabiol			
Percent reporting recent use	52%	42%	47%
Users use per month (mean, SEM)	4.7 (1.6)	7.0 (2.1)	5.8 (1.3)
Cancer prognosis at time of enrollment			
Possibility of recurrence	32%	38%	35%
Recurrent/metastatic (>2yr anticipated survival)	32%	42%	37%
Recurrent/metastatic (<2yr anticipated survival)	36%	19%	27%
Psychiatric symptoms[a]			
Depressed mood	72%	65%	69%
Anxiety	68%	58%	63%
Prior use of medication for anxiety or depression[b]	52%	50%	51%

+There were no significant differences between the two dose sequence groups on any demographic variable (*t*-tests and chi-square tests with continuous and categorical variables, respectively).

[a]Psychiatric symptom classification was based on SCID (DSM-IV) diagnoses. All had a DSM-IV diagnosis: chronic adjustment disorder with anxiety (11 participants), chronic adjustment disorder with mixed anxiety and depressed mood (11), dysthymic disorder (5), generalized anxiety disorder (GAD) (5), major depressive disorder (MDD) (14), or a duel diagnosis of GAD and MDD (4), or GAD and dysthymic disorder (1). Depressed mood was defined as meeting criteria for MDD, dysthymic disorder, or adjustment disorder with anxiety and depressed mood, chronic. Anxiety was defined as meeting criteria for GAD, adjustment disorder with anxiety, chronic, or adjustment disorder with anxiety and depressed mood, chronic.

[b]Data in this row refer to percentage of participants who had received antidepressant or anxiolytic medication after the cancer diagnosis but had terminated the medication sometime before study enrollment because they had found it to be unsatisfactory.

know the specific drug conditions to be tested. For these reasons, in the present study a low dose of psilocybin was compared with a high dose of psilocybin, and participants and monitors were given instructions that obscured the actual dose conditions to be tested. Specifically, they were told that psilocybin would be administered in both sessions, the psilocybin doses administered in the two sessions might range anywhere from very low to high, the doses in the two sessions might or might not be the same, sensitivity to psilocybin dose varies widely across individuals, and that at least one dose would be moderate to high. Participants and monitors were further strongly encouraged to try to attain maximal therapeutic and personal benefit from each session.

Dose conditions. The study compared a high psilocybin dose (22 or 30 mg/70 kg) with a low dose (1 or 3 mg/70 kg) administered in identically appearing capsules. When this study was designed, we had little past experience with a range of psilocybin doses. We decreased the high dose from 30 to 22 mg/70 kg after two of the first three participants who received a high dose of 30 mg/70 kg were discontinued from the study (one from vomiting shortly after capsule administration and one for personal reasons). Related to this decision, preliminary data from a dose-effect study in healthy participants suggested that rates of psychologically challenging experiences were substantially greater at 30 than at 20 mg/70 kg (Griffiths et al., 2011). The low dose of psilocybin was decreased from 3 to 1 mg/70 kg after 12 participants because data from the same dose-effect study showed significant psilocybin effects at 5 mg/70 kg, which raised concern that 3 mg/70 kg might not serve as an inactive placebo.

Outcome measures

Cardiovascular measures and monitor ratings assessed throughout the session. Ten minutes before and 30, 60, 90, 120, 180, 240, 300, and 360 min after capsule administration, blood pressure, heart rate, and monitor ratings were obtained as described previously (Griffiths et al., 2006). The two session monitors completed the Monitor Rating Questionnaire, which involved rating or scoring several dimensions of the participant's behavior or mood. The dimensions, which are expressed as peak scores in Table 2, were rated on a 5-point scale from 0 to 4. Data were the mean of the two monitor ratings at each time-point.

Table 2. Peak effects on cardiovascular measures and session monitor ratings of participant behavior and mood assessed throughout the session+.

Measure	Low dose	High dose
Cardiovascular measures (peak effects)		
Systolic blood pressure (mm Hg)	142.20 (2.45)	155.26 (2.87)***
Diastolic blood pressure (mm Hg)	82.90 (1.35)	89.68 (1.21)***
Heart rate (beats per minute)	78.86 (2.17)	84.06 (2.36)***
Session monitor ratings (peak effects)[a]		
Overall drug effect	1.37 (0.09)	2.90 (0.07)***
Unresponsive to questions	0.13 (0.07)	0.70 (0.12)***
Anxiety or fearfulness	0.50 (0.10)	0.93 (0.15)**
Distance from ordinary reality	0.94 (0.12)	2.68 (0.10)***
Ideas of reference/paranoid thinking	0.05 (0.03)	0.14 (0.05)***
Yawning	0.33 (0.11)	1.28 (0.26)***
Tearing/crying	0.66 (0.14)	2.01 (0.25)***
Nausea/vomiting	0.11 (0.04)	0.44 (0.10)**
Visual effects with eyes open	0.32 (0.09)	1.83 (0.17)***
Visual effects with eyes closed	0.93 (0.09)	1.75 (0.07)***
Spontaneous motor activity	1.12 (0.15)	1.86 (0.30)*
Restless/fidgety	0.83 (0.12)	1.28 (0.15)**
Joy/intense happiness	0.69 (0.12)	1.90 (0.14)***
Peace/harmony	1.08 (0.13)	2.01 (0.13)***
Psychological discomfort	0.34 (0.08)	0.91 (0.15)***
Physical discomfort	0.31 (0.08)	0.62 (0.11)**

+Data are means (SEM) for peak effects during sessions after low dose (n=50) or high dose (n=50) psilocybin collapsed across the two dose sequence groups. Asterisks indicate significant differences from the low dose (*p<0.05, **p<0.01, ***p<0.001).

[a]Maximum possible scores for all monitor ratings were 4 except for visual effects with eyes closed which was 2.

Subjective drug effect measures assessed 7 h after psilocybin administration. When psilocybin effects had subsided, participants completed four questionnaires: Hallucinogen Rating Scale (HRS) (Strassman et al., 1994); 5-Dimension Altered States of Consciousness (5D-ASC) (Dittrich, 1998); Mysticism Scale (Experience-specific 9-point scale) (Hood et al., 2001, 2009); and the States of Consciousness Questionnaire (SOCQ) (Griffiths et al., 2006). Thirty items on the SOCQ comprise the Mystical Experience Questionnaire (MEQ30), which was shown sensitive to mystical-type subjective effects of psilocybin in laboratory studies as well as survey studies of recreational use of psilocybin mushrooms (Barrett et al., 2015; MacLean et al., 2012). Four factor scores (Mystical, Positive mood, Transcendence of time and space, and Ineffability) and a mean total score (the mean of all 30 items) were assessed.

Therapeutically relevant measures assessed at Baseline, 5 weeks after each session, and 6-month follow-up. Seventeen measures focused on mood states, attitudes, disposition, and behaviors thought to be therapeutically relevant in psychologically distressed cancer patients were assessed at four time-points over the study: immediately after study enrollment (Baseline assessment), about 5 weeks (mean 37 days) after each session (Post-session 1 and 2 assessments), and about 6 months (mean 211 days) after session 2 (6-month follow-up).

The two primary therapeutic outcome measures were the widely used clinician-rated measures of depression, GRID-HAM-D-17 (ISCDD, 2003) and anxiety, HAM-A assessed with the SIGH-A (Shear et al., 2001). For these clinician-rated measures, a clinically significant response was defined as ⩾50% decrease in measure relative to Baseline; symptom remission was defined as ⩾50% decrease in measure relative to Baseline and a score of ⩽7 on the GRID-HAMD or HAM-A (Gao et al., 2014; Matza et al., 2010).

Fifteen secondary measures focused on psychiatric symptoms, moods, and attitudes: BDI, self-rated depression measure (Beck and Steer, 1987); HADS, self-rated separate measures of depression and anxiety, and a total score (Zigmond and Snaith, 1983); STAI, self-rated measure of state and trait anxiety separately (Spielberger, 1983); POMS, Total Mood Disturbance Subscale, self-rated dysphoric mood measure (McNair et al., 1992); BSI, self-rated psychiatric symptoms (Derogatis, 1992); MQOL, self-rated measure of overall quality of life (total score) and meaningful existence (existential subscale) during life-threatening illness (Cohen et al., 1995); LOT-R, self-rated optimism measure associated with illness (Scheier and Carver, 1985); LAP-R Death Acceptance, self-rated scale assessing absence of anxiety about death (Reker, 1992); Death Transcendence Scale, self-rated measure of positive attitudes about death (VandeCreek, 1999); Purpose in Life Test, self-rated measure of life meaningfulness (McIntosh, 1999); and LAP-R Coherence, self-rated scale assessing logically integrated understanding of self, others, and life in general (Reker, 1992).

Community observer-rated changes in participant behavior and attitudes assessed at Baseline, 5 weeks after Session 2, and 6-month follow-up. Structured telephone interviews with community observers (e.g. family members, friends, or work colleagues) provided ratings of participant attitudes and behavior reflecting healthy psychosocial functioning (Griffiths et al., 2011). The interviewer provided no information to the rater about the participant or the nature of the research study. The structured interview (Community Observer Questionnaire) consisted of asking the rater to rate the participant's behavior and attitudes using a 10-point scale (from 1 = not at all, to 10 = extremely) on 13 items reflecting healthy psychosocial functioning: inner peace; patience; good-natured humor/playfulness; mental flexibility; optimism; anxiety (scored negatively); interpersonal perceptiveness and caring; negative expression of anger (scored negatively); compassion/social concern; expression of positive emotions (e.g. joy, love, appreciation); self-confidence; forgiveness of others; and forgiveness of self. On the first rating occasion, which occurred soon after acceptance into the study, raters were instructed to base their ratings on observations of and conversations with the participant over the past 3 months. On two subsequent assessments, raters were told their previous ratings and were instructed to rate the participant based on interactions over the last month (post-session 2 assessment) or since beginning in the study (6-month follow-up). Data from each interview with each rater were calculated as a total score. Changes in each participant's behavior and attitudes after drug sessions were expressed as a mean change score (i.e. difference score) from the baseline rating across the raters. Of 438 scheduled ratings by community observers, 25 (<6%) were missed due to failure to return calls or to the rater not having contact with the participant over the rating period.

Spirituality measures assessed at Baseline, 5 weeks after Session 2, and 6-month follow-up. Three measures of spirituality were assessed at three time-points: Baseline, 5 weeks after session 2, and at the 6-month follow-up: FACIT-Sp, a self-rated measure of the spiritual dimension of quality of life in chronic illness (Peterman et al., 2002) assessed on how the participant felt "on average"; Spiritual-Religious Outcome Scale, a three-item measure used to assess spiritual and religious changes during illness (Pargament et al., 2004); and Faith Maturity Scale, a 12-item scale assessing the degree to which a person's priorities and perspectives align with "mainline" Protestant traditions (Benson et al., 1993).

Persisting effects of the psilocybin session assessed 5 weeks after each session and 6-month follow-up. The Persisting Effects Questionnaire assessed self-rated positive and negative changes in attitudes, moods, behavior, and spiritual experience attributed to the most recent psilocybin session (Griffiths et al., 2006, 2011). At the 6-month follow-up, the questionnaire was completed on the basis of the high-dose session, which was identified as the session in which the participant experienced the most pronounced changes in their ordinary mental processes. Twelve subscales (described in Table 8) were scored.

The questionnaire included three final questions (see Griffiths et al. 2006 for more specific wording): (1) How personally meaningful was the experience? (rated from 1 to 8, with 1 = no more than routine, everyday experiences; 7 = among the five most meaningful experiences of my life; and 8 = the single most meaningful experience of my life). (2) Indicate the degree to which the experience was spiritually significant to you? (rated from 1 to 6, with 1 = not at all; 5 = among the five most spiritually significant experiences of my life; 6 = the single most spiritually significant experience of my life). (3) Do you believe that the experience and your contemplation of that experience have led to change in your current sense of personal well-being or life satisfaction? (rated from +3 = increased very much; +2 = increased moderately; 0 = no change; –3 = decreased very much).

Statistical analysis

Differences in demographic data between the two dose sequence groups were examined with *t*-tests and chi-square tests with continuous and categorical variables, respectively.

Data analyses were conducted to demonstrate the appropriateness of combining data for the 1 and 3 mg/70 kg doses in the low-dose condition and for including data for the one participant who received 30 mg/70 kg. To determine if the two different psilocybin doses differed in the low-dose condition, *t*-tests were used to compare participants who received 3 mg/70 kg ($n = 12$) with those who received 1 mg/70 kg ($n = 38$) on participant ratings of peak intensity of effect (HRS intensity item completed 7 h after administration) and peak monitor ratings of overall drug effect across the session. Because neither of these were significantly different, data from the 1 and 3 mg/70 kg doses were combined in the low-dose condition for all analyses.

Of the 50 participants who completed the high-dose condition, one received 30 mg/70 kg and 49 received 22 mg/70 kg. To determine if inclusion of the data from the one participant who received 30 mg/70 kg affected conclusions about the most therapeutically relevant outcome measures, the analyses for the 17 measures shown in Tables 4 and 5 were conducted with and without that participant. Because there were few differences in significance (72 of 75 tests remained the same), that participant's data were included in all the analyses.

To examine acute drug effects from sessions, the drug dose conditions were collapsed across the two dose sequence groups. The appropriateness of this approach was supported by an absence of any significant group effects and any group-by-dose interactions on the cardiovascular measures (peak systolic and diastolic pressures and heart rate) and on several key monitor- and participant-rated measures: peak monitor ratings of drug strength and joy/intense happiness, and end-of-session participant ratings on the Mysticism Scale.

Six participants reported initiating medication treatment with an anxiolytic (2 participants), antidepressant (3), or both (1) between the Post-session 2 and the 6-month follow-up assessments. To determine if inclusion of these participants affected statistical outcomes in the analyses of the 6-month assessment, the analyses summarized in Tables 4, 5, 6, 7 and 8 were conducted with and without these six participants. All statistical outcomes remained identical. Thus, data from these six participants were retained in the data analyses.

For cardiovascular measures and monitor ratings assessed repeatedly during sessions, repeated measures regressions were conducted in SAS PROC MIXED using an AR(1) covariance structure and fixed effects of dose and time. Planned comparison *t*-tests were used to assess differences between the high- and low-dose condition at each time-point.

Peak scores for cardiovascular measures and monitor ratings during sessions were defined as the maximum value from pre-capsule to 6 h post-capsule. These peak scores and the end-of-session ratings (Tables 2 and 3) were analyzed using repeated measures regressions in SAS PROC MIXED with a CS covariance structure and fixed effects of group and dose.

For the analyses of continuous measures described below, repeated measures regressions were conducted in SAS PROC MIXED using an AR(1) covariance structure and fixed effects of group and time. Planned comparison *t*-tests (specified below) from these analyses are reported. For dichotomous measures, Friedman's Test was conducted in SPSS for both the overall analysis and planned comparisons as specified below. All results are expressed as unadjusted scores.

For the measures that were assessed in the two dose sequence groups at Baseline, Post-session 1, Post-session 2, and 6 months (Tables 4 and 5), the following planned comparisons most relevant to examining the effects of psilocybin dose were conducted: Between-group comparisons at Baseline, Post 1, and Post 2; and within-group comparisons of Baseline versus Post 1 in both dose sequence groups, and Post 1 versus Post 2 in the Low-Dose-1st (High-Dose-2nd) Group. A planned comparison between Baseline and 6 months collapsed across groups was also conducted. Effects sizes were calculated using Cohen's *d*.

For measures assessed only at Baseline, Post 2, and 6 months (Table 7), between-group planned comparisons were conducted at Baseline, Post 2, and 6 months. Because measures assessed only at these time-points cannot provide information about the psilocybin dose, data were collapsed across the two dose sequence groups and planned comparisons were conducted comparing Baseline with Post 2 and Baseline with 6 months.

Table 3. Participant ratings on questionnaires completed 7 hours after psilocybin administration+.

Questionnaire and subscale description	Low dose (post-session)	High dose (post-session)
Hallucinogen Rating Scale (HRS)		
Intensity	36.47 (2.78)	63.76 (2.34)***
Somesthesia	15.38 (1.55)	35.62 (2.75)***
Affect	23.79 (2.13)	44.60 (2.54)***
Perception	12.92 (1.76)	41.18 (2.78)***
Cognition	18.88 (2.09)	43.08 (2.54)***
Volition	30.81 (2.02)	37.06 (1.88)*
5 Dimension Altered States of Consciousness (5D-ASC)		
Oceanic boundlessness (OBN)	26.86 (3.73)	63.99 (3.78)***
Dread of ego dissolution (DED)	6.89 (1.50)	19.21 (2.38)***
Visionary restructuralization (VRS)	22.41 (2.99)	61.16 (3.48)***
Auditory alterations (AUA)	6.72 (1.87)	14.88 (2.18)***
Vigilance reduction (VIR)	22.74 (2.70)	30.85 (2.24)**
Mystical Experience Questionnaire (MEQ30)		
Mystical	24.34 (3.83)	59.58 (4.22)***
Transcendence of time and space	22.38 (2.90)	62.08 (3.38)***
Positive mood	35.84 (4.00)	69.82 (3.82)***
Ineffability	30.80 (4.49)	74.46 (3.67)***
Total	26.90 (3.44)	63.64 (3.56)***
Mysticism Scale (M scale)		
Interpretation	48.95 (3.54)	71.45 (2.24)***
Introvertive	44.53 (3.21)	71.20 (2.14)***
Extrovertive	37.48 (3.19)	64.58 (2.81)***
Total	49.36 (3.51)	77.38 (2.40)***

+All data are expressed as a percentage of maximum possible score. Data are means (1 SEM) for questionnaires completed 7 h after the low-dose (n = 50) and high-dose (n = 50) sessions collapsed across the two dose sequence groups. Asterisks indicate significant differences from the low dose (*p<0.05, **p<0.01, ***p<0.001).

For participant ratings of persisting effects attributed to the session (e.g. Table 8), planned comparisons for continuous and dichotomous measures were conducted between: (1) ratings at 5 weeks after the low versus high-dose sessions; (2) ratings of low dose at 5 weeks versus ratings of high dose at the 6-month follow-up; (3) ratings of high dose at 5 weeks versus ratings of high dose at the 6-month follow-up.

As described above, clinician-rated measures of depression (GRID-HAMD) and anxiety (HAM-A) were analyzed as continuous measures. In addition for both measures, a clinically significant response was defined as ⩾50% decrease in measure relative to Baseline; symptom remission was defined as ⩾50% decrease in measure relative to Baseline and a score of ⩽7. Planned comparisons were conducted via independent z-tests of proportions between the two dose sequence groups at Post-session 1, Post-session 2, and 6 months. To determine if effects were sustained at 6 months, planned comparisons were also conducted via dependent z-tests of proportions between Post-session 2 versus 6 months in the Low-Dose-1st (High-Dose-2nd) Group, and between Post-session 1 versus 6 months in the High-Dose-1st (Low-Dose-2nd) Group.

Exploratory analyses used Pearson's correlations to examine the relationship between total scores on the Mystical Experience Questionnaire (MEQ30) assessed at the end of session 1 and enduring effects assessed 5 weeks after session 1. The Post-session 1 measures were ratings on three items from the Persisting Effects Questionnaire (meaningfulness, spiritual significance, and life satisfaction) and 17 therapeutically relevant measures assessed at Baseline and Post 1 (Tables 4 and 5) expressed as difference from baseline scores. Significant relationships were further examined using partial correlations to control for end-of-session participant-rated "Intensity" (item 98 from the HRS). To examine MEQ30 scores as a mediator of the effect of psilocybin dose on therapeutic effects, a bootstrap analysis was done using the PROCESS macro (Hayes, 2013) in SPSS. Bootstrapping is a non-parametric method appropriate for small samples, which was used to estimate 95% confidence intervals for the mediation effect. The PROCESS macro also calculated direct effects on outcome for both group effects and MEQ30.

Results

Adverse effects

No serious adverse events attributed to psilocybin administration occurred. A number of adverse events occurred during psilocybin sessions, none of which were deemed to be serious. Except as noted below, all of these adverse events had resolved fully by the end of the sessions. Consistent with previous research (Griffiths et al., 2006, 2011), there were transient moderate increases in systolic and/or diastolic blood pressure after psilocybin. In this study, an episode of elevated systolic blood pressure (>160 mm Hg at one or more time-point) occurred in 34% of participants in the high-dose session and 17% of participants in the low-dose session. An episode of elevated diastolic blood pressure (>100 mm Hg at one or more time-point) occurred in 13% of participants in the high-dose session and 2% of participants in the low-dose session. None of these episodes met criteria for medical intervention. Nausea or vomiting occurred in 15% of participants in the high-dose session and none in the low-dose session. An episode of physical discomfort (any type) occurred in 21% of participants in the high-dose session and 8% in the low-dose session. Also consistent with previous research (Griffiths et al., 2006, 2011), transient episodes of psychological distress during psilocybin sessions (as rated by session monitors) were more common after the high dose than the low dose. Psychological discomfort (any type) occurred in 32% of participants in the high-dose session and 12% in the low-dose session. An episode of anxiety occurred in 26% of participants in the high-dose session and 15% in the low-dose session. One participant had a transient episode of paranoid ideation (2% of high-dose sessions). There were no cases of hallucinogen persisting perception disorder or prolonged psychosis. One participant reported mild headache starting toward the end of the high-dose session and lasting until 9 p.m. that evening. Of the 11 participants for whom headache was assessed on the day after sessions, two reported a delayed moderate headache after the high-dose session.

Integrity of blinding procedures

After all psilocybin sessions had been completed, the eight study staff members who had served as primary monitors or as assistant monitors for four or more participants completed a questionnaire

Table 4. Effects of psilocybin on the 11 therapeutically relevant outcome measures assessed at Baseline, Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6 months follow-up that fulfilled conservative criteria for demonstrating an effect of psilocybin+.

Measure	Group	Assessment time-point			
		Baseline[a]	Post-session 1[b]	Post-session 2[c]	6 months[d]
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	22.32 (0.88)	*14.80 (1.45)*	6.50 (0.86)***	6.95 (1.24)
	High-Dose-1st (Low-Dose-2nd)	22.84 (0.97)	*6.64 (1.04)***	6.52 (1.44)	6.23 (1.30)
Beck Depression Inventory (BDI)	Low-Dose-1st (High-Dose-2nd)	18.40 (1.09)	*12.92 (1.58)*	8.17 (1.24)***	8.00 (1.50)
	High-Dose-1st (Low-Dose-2nd)	17.77 (1.61)	*7.00 (1.39)***	5.80 (1.41)	6.17 (1.26)
HADS Depression	Low-Dose-1st (High-Dose-2nd)	9.48 (0.71)	*6.04 (0.79)*	4.57 (0.73)*	4.64 (0.72)
	High-Dose-1st (Low-Dose-2nd)	9.81 (0.69)	*3.92 (0.74)**	4.28 (0.89)	3.46 (0.66)
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	25.68 (0.89)	*16.64 (1.53)*	8.92 (1.14)***	7.95 (1.19)
	High-Dose-1st (Low-Dose-2nd)	25.73 (1.11)	*8.48 (1.16)****	7.52 (1.27)	7.04 (1.17)
STAI-Trait Anxiety	Low-Dose-1st (High-Dose-2nd)	47.46 (1.62)	*40.48 (2.11)*	35.48 (2.05)**	36.83 (2.08)
	High-Dose-1st (Low-Dose-2nd)	47.73 (1.91)	*34.64 (1.84)**	34.28 (2.25)	35.32 (2.18)
POMS Total Mood Disturbance	Low-Dose-1st (High-Dose-2nd)	51.72 (6.35)	42.48 (7.72)	21.09 (5.81)***	23.50 (6.57)
	High-Dose-1st (Low-Dose-2nd)	56.93 (5.33)	*18.96 (5.78)***	17.14 (6.35)	12.52 (5.36)
Brief Symptom Inventory (BSI)	Low-Dose-1st (High-Dose-2nd)	41.76 (4.40)	*33.74 (4.47)*	26.08 (4.53)*	23.50 (3.85)
	High-Dose-1st (Low-Dose-2nd)	40.19 (3.71)	*18.08 (3.62)***	16.48 (3.77)	14.35 (3.35)
MQOL (Overall Quality of Life)	Low-Dose-1st (High-Dose-2nd)	5.69 (0.24)	6.17 (0.32)	6.90 (0.34)**	6.88 (0.37)
	High-Dose-1st (Low-Dose-2nd)	5.32 (0.29)	*7.14 (0.29)**	7.46 (0.34)	7.65 (0.36)
MQOL (Meaningful Existence)	Low-Dose-1st (High-Dose-2nd)	6.03 (0.30)	6.10 (0.39)	7.30 (0.35)***	7.29 (0.31)
	High-Dose-1st (Low-Dose-2nd)	5.43 (0.29)	*7.23 (0.33)**	7.30 (0.38)	7.62 (0.35)
LAP-R Death Acceptance	Low-Dose-1st (High-Dose-2nd)	28.05 (2.04)	29.14 (2.25)	34.95 (1.92)***	34.95 (1.52)
	High-Dose-1st (Low-Dose-2nd)	29.09 (2.07)	*36.17 (1.59)**	35.13 (1.90)	36.25 (1.59)
LOT-R (Optimism)	Low-Dose-1st (High-Dose-2nd)	13.56 (0.97)	13.60 (1.23)	15.96 (1.12)**	16.68 (1.14)
	High-Dose-1st (Low-Dose-2nd)	14.15 (0.97)	*17.23 (0.67)**	17.16 (0.99)	17.43 (0.92)

+Numerical data show means (SEM) for outcome measures in the two dose sequence groups: (1) those that received a low dose on the 1st session and a high dose on the 2nd (n = 25, 25, 24, and 22 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively), and (2) those that received a high dose on 1st session and a low dose on the 2nd (n = 26, 25 or 26, 25, and 24 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively). Data are shown for the 11 measures that fulfilled the most conservative criteria for demonstrating psilocybin effects (i.e. showing a significant between-group difference at the Post-session 1 assessment as well as a difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group). Results for the measures not fulfilling these criteria are shown in Table 5.

[a]In this column (Baseline), there were no significant differences between groups.

[b]In this column, italic font indicates a within-group significant difference from Baseline (p<.05, planned comparison); asterisks indicate significant differences between groups (*p<0.05, **p<0.01, ***p<0.001, planned comparisons); between groups effect size (Cohen's d as absolute values) for the 11 measures from top to bottom were: 1.30, 0.81, 0.56, 1.23, 0.60, 0.70, 0.78, 0.65, 0.65, 0.97, and 0.75.

[c]In this column, there were no significant differences between groups; asterisks indicate significant differences between the Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group (*p<0.05, **p<0.01, ***p<0.001, planned comparisons); effect size (Cohen's d as absolute values) for the 11 measures from top to bottom were: 1.33, 0.69, 0.40, 1.10, 0.50, 0.64, 0.35, 0.46, 0.66, 0.68, and 0.41.

[d]The difference between Baseline and 6 months, collapsed across groups, was significant for all 11 measures (p<0.001, planned comparison); effect size (Cohen's d as absolute values) for the 11 measures from top to bottom were: 2.98,1.63, 1.65, 3.40, 1.20, 1.26, 1.17, 1.14, 1.12, 0.84, and 0.66.

that asked about their understanding of the experimental design. Although all correctly believed that psilocybin had been administered, five of eight made incorrect inferences about the study design or procedures, including possible administration of three or more dose levels of psilocybin across different participants (four monitors), an inactive placebo (one monitor), other psychoactive compounds such as dextromethorphan (one monitor), or only low psilocybin doses (one monitor).

At the end of each session day, monitors rated their guess of the magnitude of drug dose administered in the capsule that day on a 10 cm line. Although, as expected, the mean (±SE) monitor rating of the dose magnitude of the high psilocybin dose was significantly larger than the low dose (7.0±0.29 vs. 1.7±0.21, p<0.001, planned comparison), the distributions of ratings overlapped, with more than 13% of the high-dose sessions being rated as 4 or less and more than 12% of the low-dose sessions being rated as 4 or more. Overall, we conclude that the blinding procedures provided some protection against a priori monitor expectancy strongly determining outcomes of the psilocybin dose manipulation.

Outcome measures

Psilocybin produced orderly dose- and time-related increases on blood pressure, heart rate, and all 16 monitor-rated dimensions of the participant's behavior or mood assessed throughout sessions, with a generally similar time-course in both dose conditions (see Figure 2 for illustrative time-course measures). Significant differences between the dose conditions generally first occurred at 30- or 60-min, with the high dose usually showing peak effects from 90–180 min and decreasing toward pre-drug levels over the remainder of the session. Table 2 shows mean peak effects for these measures.

End-of-session measures that assessed subjective experiences during the session were significantly greater after the high than the low dose (Table 3).

Table 5. Effects of psilocybin on six therapeutically relevant outcome measures assessed at Baseline, Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6 months that did not fulfill conservative criteria for demonstrating an effect of psilocybin+.

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

+Numerical data show means (1 SEM) for primary outcome measures in the two dose sequence groups: (1) those that received a low dose on the 1st session and a high dose on the 2nd (n = 25, 25, 24, and 22 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively), and (2) those that received a high dose on 1st session and a low dose on the 2nd (n = 26, 26, 25, and 24 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively). Data are shown for the six measures that did not fulfill the most conservative criteria for demonstrating psilocybin effects (i.e. did not show a significant between-group difference at the Post-session 1 assessment as well as a significant difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group).

[a]In this column, there were no significant differences between groups.

[b]In this column, italic font indicates a within-group significant difference from Baseline (p<0.05, planned comparison); there were no significant between-group differences.

[c]In this column, there were no significant differences between groups; asterisks indicate significant differences between the Post-session 1 and Post-session 2 assessments in the Low-Dose-1st (High-Dose-2nd) Group (*p<0.05, **p<0.01, planned comparisons); effect size (Cohen's d as absolute values) for the five significant measures (HADS total, STAI State Anxiety, Death Transcendence Scale, Purpose in Life, and LAP-R Coherence, respectively were: 0.51, 0.41, 0.46, 0.28, and 0.49.

[d]The difference between Baseline and 6 months, collapsed across groups, was significant for all six measures (p<0.001, planned comparison); effect size (Cohen's d as absolute values) for the six measures from top to bottom were: 2.34, 2.15, 1.25, 0.58, 0.85, and 0.90.

Table 6. Percentage of participants with clinically significant response rate and symptom remission rate as assessed with the clinician-rated measures of depression and anxiety+[a].

Measure	Group	Assessment time-point					
		Post-session 1		Post-session 2		6 months[b]	
		Clinical response	Symptom remission	Clinical response	Symptom remission	Clinical response	Symptom remission
GRID-HAMD-17 (Depression)	Low-Dose-1st (High-Dose-2nd)	32%	16%	75%	58%	77%	59%
	High-Dose-1st (Low-Dose-2nd)	92%***	60%**	84%	68%	79%	71%
HAM-A (Anxiety)	Low-Dose-1st (High-Dose-2nd)	24%	12%	83%	42%	82%	50%
	High-Dose-1st (Low-Dose-2nd)	76%***	52%**	80%	60%	83%	63%

+ Data are percentage of participants fulfilling criteria at Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6 months. Clinical response was defined as ⩾50% decrease in measure relative to Baseline; Symptom remission was defined as ⩾50% decrease in measure relative to Baseline and a score of ⩽7 on GRID-HAMD-17 or HAM-A. For the Post-session 1, Post-session 2, and 6-month time-points, respectively, the number of participants was 25, 24, and 22 in the Low-Dose-1st (High-Dose-2nd) Group, and 25, 25, and 24 in the High-Dose-1st (Low-Dose-2nd) Group.

[a]Within each data column, asterisks indicate significant differences between groups (*p<0.05, **p<0.01, ***p<0.001, planned comparisons, z-tests).

[b]Effects of psilocybin on response and remission were sustained at 6 months as indicated by an absence of significant difference (p>0.05, planned comparisons, z-tests) between (1) Post-session 2 vs. 6 months in the Low-Dose-1st (High-Dose-2nd) Group and (2) Post-session 1 vs. 6 months in the High-Dose-1st (Low-Dose-2nd) Group. Overall response and remission rates were somewhat higher at 6 months when data were excluded for the six participants who initiated treatment with an antidepressant or anxiolytic between Post-session 2 and 6 months: on the GRID-HAMD-17 mean response and remission rate across the two dose sequence groups at 6 months increased from 78% to 83% and from 65% to 68%, respectively. On the HAM-A these rates increased from 83% to 85% and from 57% to 60%, respectively.

Psilocybin produced large and sustained effects on the two primary clinician-rated therapeutically relevant outcome measures as well as most of the secondary measures assessed at Baseline, 5 weeks after each session, and at 6-month follow-up. Of the 17 measures assessed, 16 showed significant effects (i.e. a between-group difference at the Post-session 1 assessment and/or

Table 7. Community observer ratings of participant attitudes and behavior, and three measures of spirituality assessed at Baseline, Post-session 2 (5 weeks after Session 2), and 6 months, collapsed across the two drug sequence groups*.

Measure	Assessment time-point		
	Baseline	Post-session 2[a]	6 months[b]
Community observer ratings of positive changes in attitudes & behavior			
Total score	81.62 (1.61)	93.79 (1.70)***	94.41 (1.66)***
FACIT-Sp – Spiritual well-being in chronic illness			
Total score (% of maximum score)	44.92 (2.71)	68.13 (3.62)***	70.79 (3.17)***
Faith Maturity Scale			
Total score (% of maximum score)	49.73 (2.71)	53.94 (3.39)*	55.56 (3.29)*
Spiritual/Religious Outcome Scale			
Total score (% maximum score)	48.53 (3.97)	64.67 (3.54)***	63.41 (3.80)***

Numerical data show means (1 SEM) for outcome measures collapsed across the two dose sequence groups (n = 51, 50, and 46 at Baseline, Post-session 2, and 6 months, respectively). The two dose sequence groups were not significantly different from each other at Baseline, Post-session 2, and 6-month assessments (planned comparisons). Asterisks indicate significant differences from Baseline (p<0.05, **p<0.01, ***p<0.001, planned comparisons).
[a]In this column, effect size (Cohen's d as absolute values) for the four measures from top to bottom were: 1.06, 1.03, 0.20, 0.61.
[b]In this column, effect size (Cohen's d as absolute values) for the four measures from top to bottom were: 1.14, 1.28, 0.28, and 0.55.

Table 8. Participant ratings of persisting effects attributed to the session on ratings completed 5 weeks after the low-dose and high-dose psilocybin sessions, and, again, retrospectively for the high-dose session 6 months after the second session+.

Questionnaire and subscale description	Assessment time-point		
	Low dose (5 weeks)	High dose (5 weeks)	High dose 6-month follow-up
Persisting Effects Questionnaire (% of maximum score)			
Positive attitudes about life	39.57 (3.91)	57.78 (3.10)***	61.17 (3.51)***
Negative attitudes about life	3.82 (0.99)	5.08 (1.54)	3.18 (0.96)
Positive attitudes about self	35.16 (3.80)	50.70 (3.46)***	54.78 (3.37)***
Negative attitudes about self	3.89 (0.86)	4.80 (1.43)	3.52 (1.16)
Positive mood changes	36.85 (3.99)	49.06 (3.45)***	55.32 (3.58)***
Negative mood changes	3.42 (1.18)	5.42 (1.57)	3.00 (1.18)
Altruistic/positive social effects	35.60 (3.79)	47.42 (3.49)***	51.11 (3.69)***
Antisocial/negative social effects	3.55 (1.11)	3.73 (1.06)	2.51 (0.90)
Positive behavior changes	48.40 (4.66)	59.60 (4.02)***	64.78 (4.03)***
Negative behavior changes	1.60 (1.27)	3.60 (1.97)	0.87 (0.61)
Increased spirituality	37.07 (4.31)	52.48 (3.88)***	57.43 (4.17)***
Decreased spirituality	1.68 (0.63)	1.88 (0.68)	1.27 (0.39)
How personally meaningful was the experience? (maximum score=8)	4.62 (0.31)	6.38 (0.20)***	6.65 (0.18)***
Top 5 most meaningful of life, including single most (% of participants)	24%	62%***	67.4%***
How spiritually significant was the experience? (maximum score=6)	3.16 (0.24)	4.46 (0.19)***	4.78 (0.17)***
Top 5 most spiritually significant of life, including single most (% of participants)	24%	66%***	69.6%***
Did the experience change your sense of well-being or life satisfaction? (maximum score=3)	1.50 (0.19)	2.20 (0.16)***	2.33 (0.14)***
Increased well-being or life satisfaction moderately or very much (% of participants)	52%	86%***	82.6%***

+Except where noted, numerical data show means (1 SEM) for persisting effects ratings 5 weeks after the low-dose session (n = 50), 5 weeks after the high-dose session (n = 50), and, again, retrospectively for the high-dose session 6 months after the second session (n = 46). There were no significant differences between ratings of the high dose at 5 weeks after the session vs. the 6-month follow-up. Asterisks indicate significant differences from ratings obtained 5 weeks after the low dose session (*p<0.05, **p<0.01, ***p<0.001, planned comparisons).

a difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st Group). Conservative criteria for concluding that psilocybin dose affected these outcomes is to consider only those measures that showed both a between-group difference at Post-session 1 and a difference between Post-session 1 and Post-session 2 assessments in the Low-Dose-1st

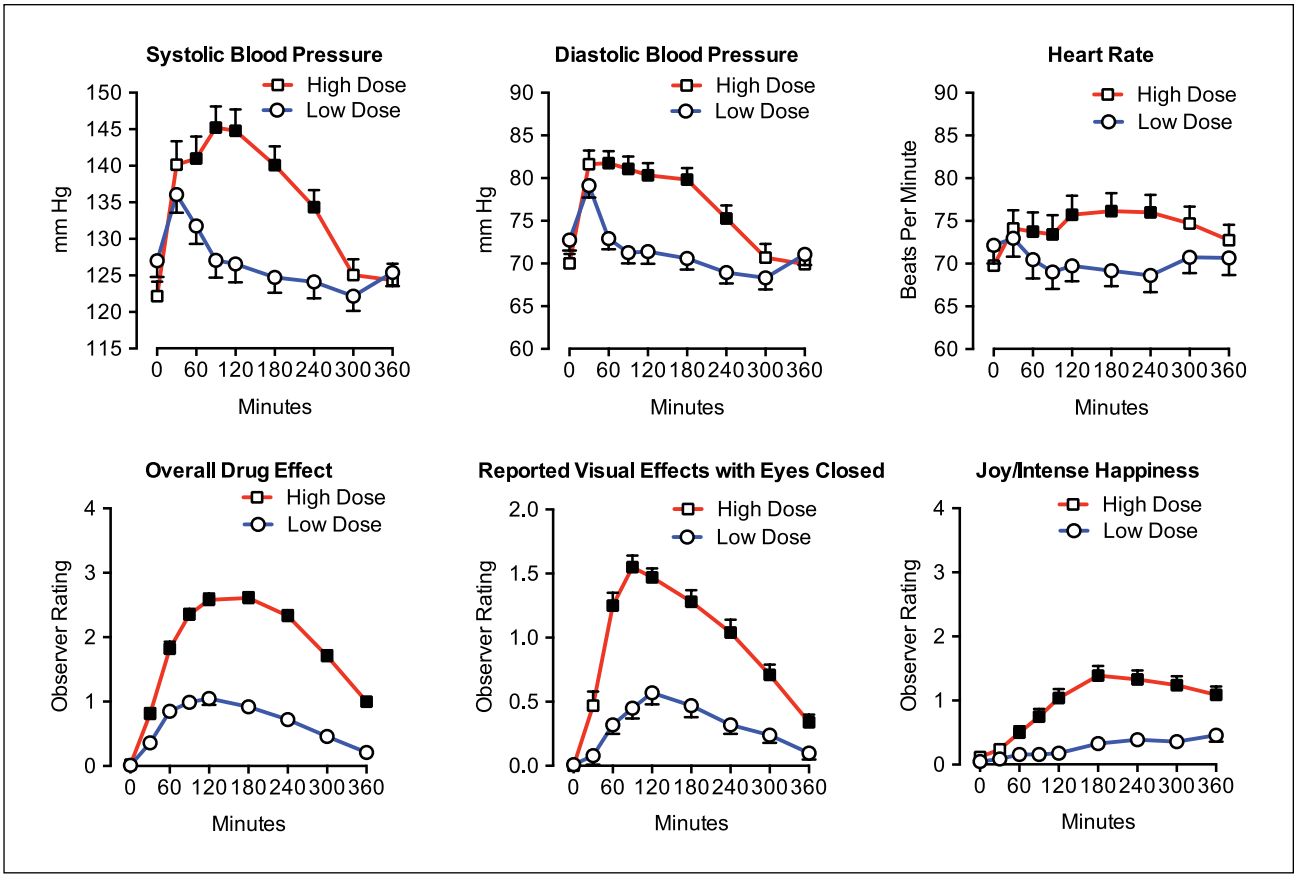

Figure 2. Within-session time-course of psilocybin effects on cardiovascular and observer-rated measures.
Cardiovascular (systolic and diastolic blood pressure, and heart rate) and observer (i.e. monitor)-rated overall drug effect, visual effects with eyes closed (as described by the participant), and joy/intense happiness. Data points show means; brackets indicate 1 SEM; circles show data after the low dose (n = 50); squares show data after the high dose (n = 50). Filled squares indicate the dose conditions were significantly different at the indicated time-point (p<0.05, planned comparisons). Y-axes for observer ratings show maximum possible scores.

Group. Table 4 shows data for the 11 measures that fulfilled these criteria and Figure 3 shows results graphically for nine of these measures. For the 11 measures, the mean effect size (Cohen's d) for the between-group difference at the Post-session 1 assessment was 0.82, for the within-group difference between Post-session 1 and Post-session 2 in the Low-Dose-1st Group was 0.66, and, for both groups combined, the difference between Baseline and 6 months was 1.55 (see Table 4 footnotes).

Table 5 presents results from six therapeutically relevant outcome measures that did not fulfill conservative criteria for demonstrating an effect of psilocybin. Although none of the measures showed a significant difference between groups at Post-session 1, five of the six showed a significant difference between Post-session 1 and Post-session 2 in the Low-Dose-1st (High-Dose-2nd) Group, and all six measures showed large significant changes in a therapeutically relevant direction (decreases in negative affect and increases in positive attitudes about death and life meaning and coherence) from Baseline to 6-Month Follow-up (mean effect size 1.35).

Rates of clinically significant response and symptom remission for the two primary outcome measures of clinician-rated symptoms of depression (GRID-HAMD-17) and anxiety (HAM-A) showed large effects of psilocybin that were sustained at 6 months (Table 6, Figure 4). For instance, 5 weeks after Session 1, 92% of participants in the High-Dose-1st Group showed a clinically significant response (i.e. ⩾50% decrease relative to Baseline) on the GRID-HAMD-17 compared with a 32% response rate in the Low-Dose-1st Group. At 6 months 79% of those in the High-Dose-1st Group continued to show a clinically significant response. Likewise, these percentages for the HAM-A were 76% and 24%, respectively, for the High-Dose 1st Group and Low-Dose-1st Group 5 weeks after Session 1, and 83% for the High-Dose-1st at 6 months. An analogous pattern of results was shown for symptom remission to normal range (i.e. ⩾50% decrease relative to Baseline and a score of ⩽7 on GRID-HAMD-17 or HAM-A), with rates of symptom remission of 60% and 52% for depression and anxiety, respectively, 5 weeks after the high psilocybin dose in Session 1, and with rates of 71% and 63%, respectively, sustained at 6 months. Collapsing across the two dose sequence groups, the overall rate of clinical response at 6 months was 78% and 83% for depression and anxiety, respectively, and the overall rate of symptom remission at 6 months for all participants was 65% and 57%, respectively.

Community observer ratings showed significant positive changes in participants' attitudes and behavior at the two post-psilocybin assessment time-points (Table 7). All three measures of spirituality showed similar increases (Table 7). As with the measures shown in Table 4, these measures show significant

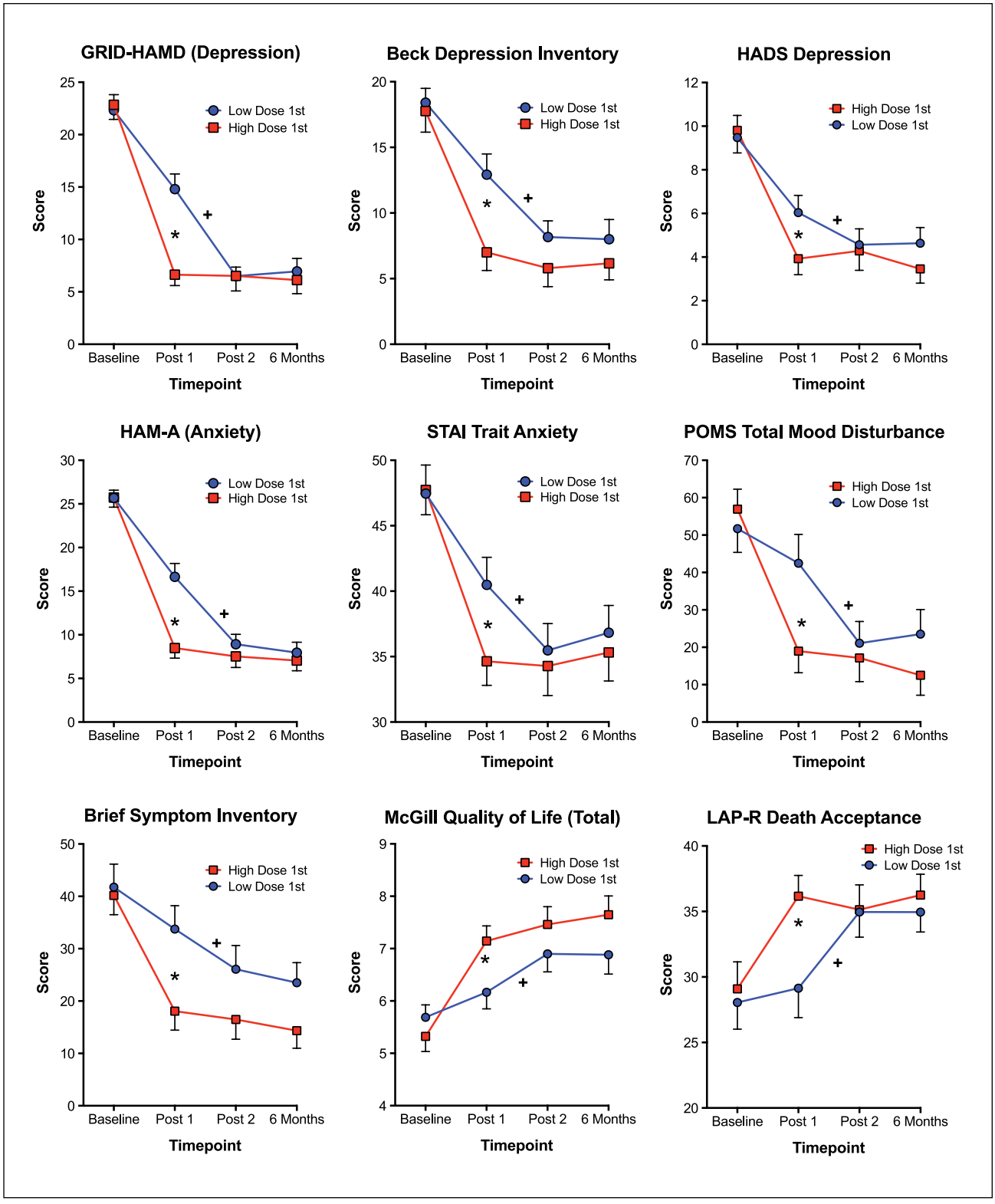

Figure 3. Effects of psilocybin on selected outcome measures that were assessed at Baseline, Post-session 1 (5 weeks after Session 1), Post-session 2 (5 weeks after Session 2), and 6-month follow-up.

Data points show means; brackets indicate 1 SEM; circles represent the group that received a low dose on the 1st session and a high dose on the 2nd session (n = 25, 25, 24, and 22 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively); squares represent the group that received a high dose on 1st session and a low dose on the 2nd session (n = 26, 26, 25, and 24 at Baseline, Post-session 1, Post-session 2, and 6 months, respectively). 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).

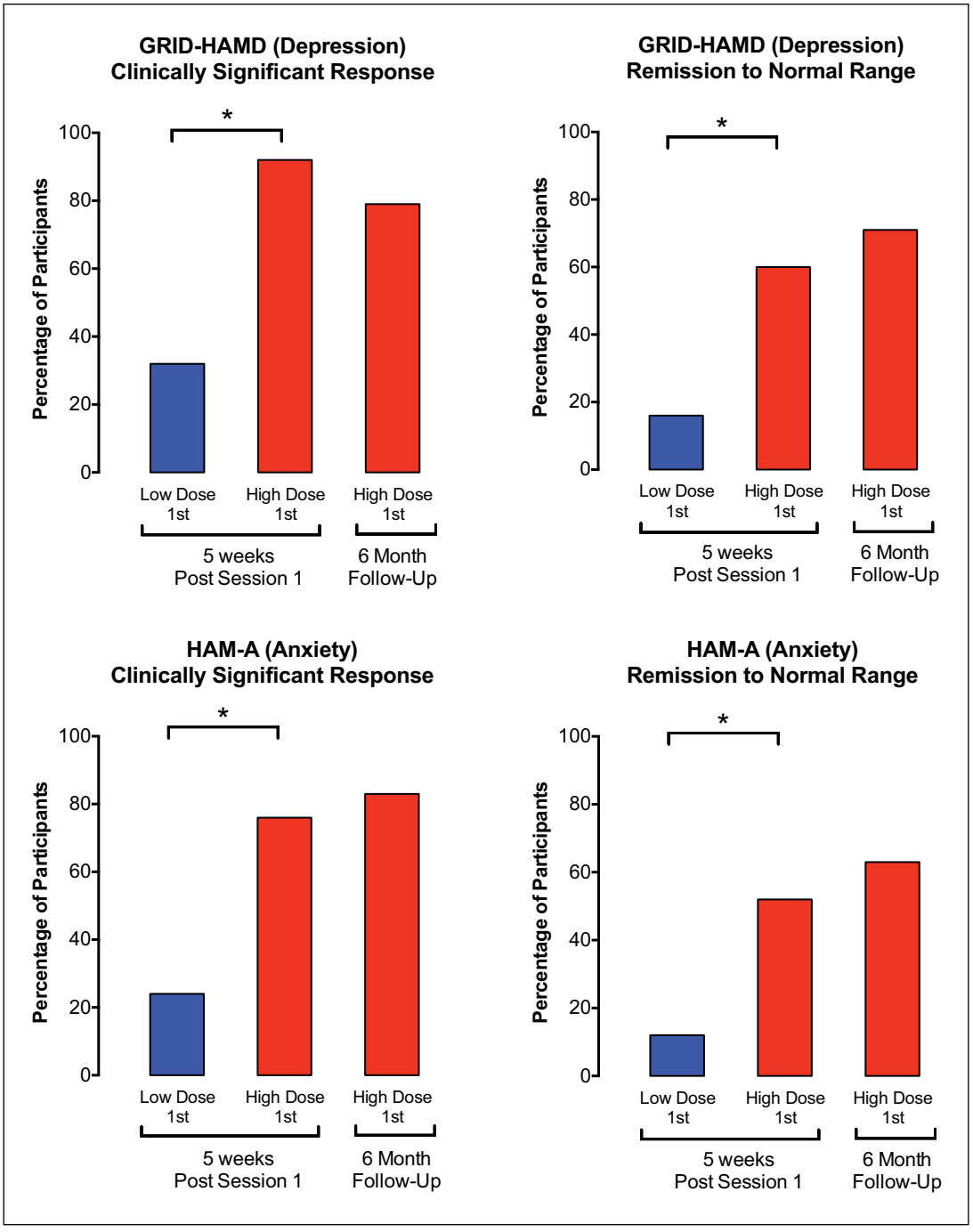

Figure 4. Effects of psilocybin on clinically significant response rate and symptom remission rate as assessed with clinician-rated measures of depression and anxiety.
Data are percentage of participants fulfilling criteria at Post-session 1 (5 weeks after Session 1) and at 6 months. Asterisks indicates that the low and high-dose groups were significantly different at 5 weeks (p>0.001); data at 6 months show these effects were sustained at follow-up. See Table 6 for other details.

changes in the expected directions at Post-session 2 that were generally sustained at the 6-month follow-up.

Table 8 shows participant ratings of persisting effects attributed to the session experiences rated 5 weeks after the low- and high-dose psilocybin sessions, and, again, for the high-dose session at the 6-month follow-up. The high dose produced significantly greater ratings of positive persisting effects on attitudes about life and self, mood changes, social effects, behavior, and spirituality. These effects were sustained at 6-month follow-up. Negative ratings of these dimensions were low and not significantly different between conditions. The high-dose experiences were rated as producing significantly greater personal meaning, spiritual significance and increased well-being or life satisfaction, with differences sustained at 6 months.

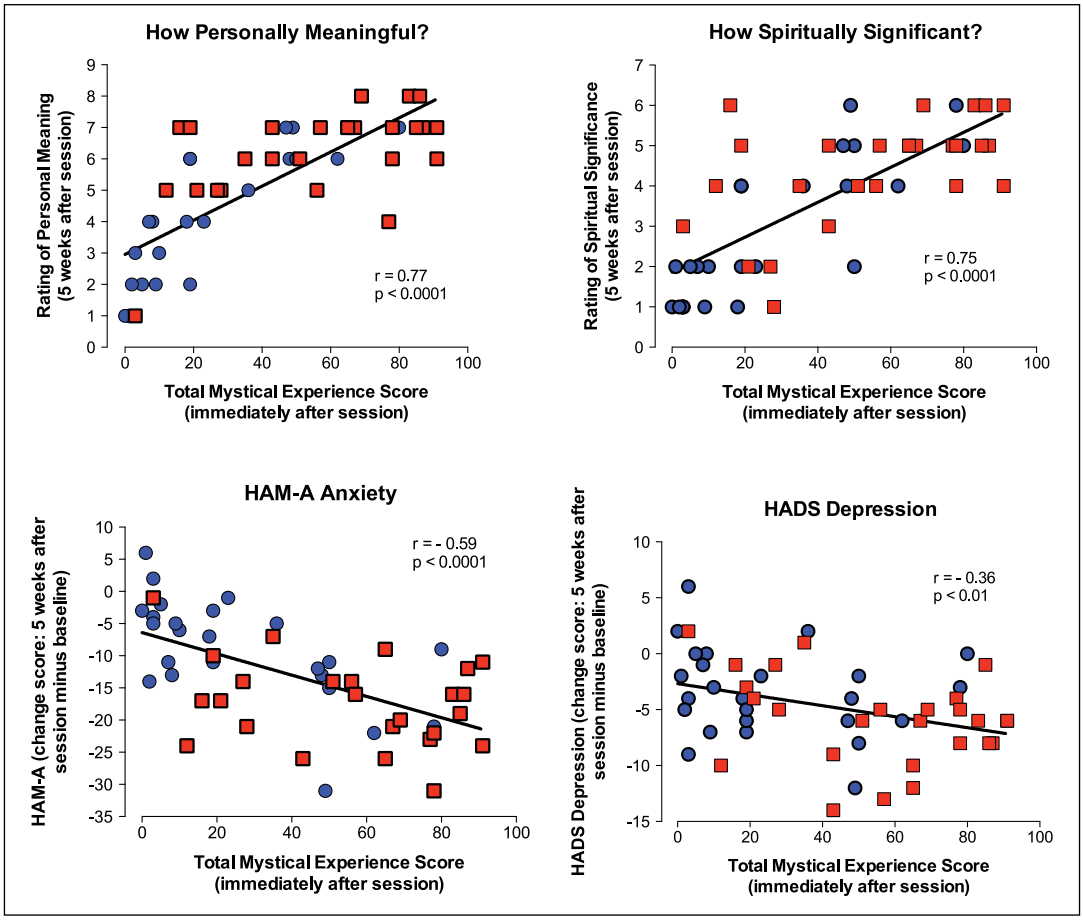

Figure 5. Relationship between the Mystical Experience Questionnaire (MEQ30) total score assessed at end of Session 1 and several illustrative outcome measures assessed 5 weeks after Session 1.

Each panel shows scores on an outcome measure assessed 5 weeks after Session 1 as a function of the total MEQ30 score obtained 7 h after psilocybin administration on Session 1. MEQ30 scores are expressed as a percentage of maximum possible score. Data points represent individual participants (n = 50 or 51); blue circles represent the group that received the low dose on the 1st session; red squares represent the group that received the high dose on the 1st session. Correlation coefficients and p-values are shown.

Mystical experience scores (MEQ30) assessed at the end of Session 1 correlated significantly with 18 of 20 measures assessed 5 weeks after the session: ratings of meaningfulness (r = 0.77), spiritual significance (r = 0.75), increased life satisfaction (r = 0.53), GRID-HAMD (r = −0.41), BDI (r = −0.30), HADS Depression (r = −0.36), HADS Total (r = −0.41), HADS Anxiety (r = −0.34), HAM-A (r = −0.59), STAI-Trait Anxiety (r = −0.31), POMS Total Mood Disturbance (r = −0.35) BSI (r = −0.38), MQOL (r = 0.32), MQOF-meaningful existence (r = 0.41), LAP-R Death Acceptance (r = 0.38), Death Transcendence Scale (r = 0.31), Purpose in Life (r = 0.29), LAP-R Coherence (r = 0.41). Figure 5 shows some of these effects. To further examine the contribution of mystical experience to these outcome measures, partial correlations were conducted to control for the participant-rated intensity of drug effect, which, like mystical experience, was assessed at the end of the session. This analysis continued to show significant effects of mystical experience on 11 of these 18 measures (meaningfulness, spiritual significance, life satisfaction, GRID-HAMD, HADS Depression, HADS Total, HADS Anxiety, HAM-A, BSI, MQOL-meaningful existence and LAP-R Coherence). Finally, a mediation analysis showed that MEQ30 score was a significant mediator of the effect of psilocybin dose on seven of these outcome measures. Point estimates and bias-corrected 95% confidence intervals for the indirect effects of the mediation analysis were: meaningfulness (1.43 [0.72–2.44]), spiritual significance (1.19 [0.59–2.10]), life satisfaction (0.60 [0.218–1.19]), HADS Anxiety (−1.50 [−3.50 to −0.33]), HADS Depression (−1.11 [−2.79 to −0.02]), HADS Total (−2.62 [−5.74 to −0.72]), and HAM-A (−3.93 [−7.88 to −1.52]).

Discussion

The present study demonstrated the efficacy of a high dose of psilocybin administered under supportive conditions to decrease symptoms of depressed mood and anxiety, and to increase quality of life in patients with a life-threatening cancer diagnosis. Eleven of 17 therapeutically relevant measures fulfilled conservative criteria for demonstrating efficacy of the high dose of psilocybin (Table 4, Figure 3). The data show that psilocybin produced large and significant decreases in clinician-rated and self-rated measures of depression, anxiety or mood disturbance, and increases in

measures of quality of life, life meaning, death acceptance, and optimism. These effects were sustained at 6 months. For the clinician-rated measures of depression and anxiety, respectively, the overall rate of clinical response at 6 months was 78% and 83% and the overall rate of symptom remission was 65% and 57%. Participants attributed to the high-dose experience positive changes in attitudes about life, self, mood, relationships and spirituality, with over 80% endorsing moderately or higher increased well-being or life satisfaction. These positive effects were reflected in significant corresponding changes in ratings by community observers (friends, family, work colleagues) of participant attitudes and behavior.

The results substantially extend the findings of a recent double-blind pilot study with a lower dose of psilocybin (14 mg/70 kg) in cancer patients that showed non-significant trends for benefits of psilocybin compared with placebo (niacin) on measures of depression and anxiety, with some significant decreases relative to baseline demonstrated at 1 to 6 months (Grob et al., 2011).

The time-course, magnitude, and qualitative features of the high dose of psilocybin on session days were consistent with those observed in previous studies in healthy volunteers (Griffiths et al., 2006, 2011; Johnson et al., 2012).

The significant association of mystical-type experience (MEQ30) during Session 1 with most of the enduring changes in therapeutic outcome measures 5 weeks later (Figure 5) is consistent with previous findings showing that such experiences on session days predict long-term positive changes in attitudes, mood, behavior, and spirituality (Garcia-Romeu et al., 2014; Griffiths et al., 2008, 2011). For most measures, this relationship continued to be significant when the intensity of overall psilocybin effect was controlled in a partial correlation analysis. This suggests that mystical-type experience per se has an important role apart from overall intensity of drug effect. Finally, a mediation analysis further suggested that mystical-type experience has a mediating role in positive therapeutic response.

The observed decreases in psychological distress and anxiety about death may relate to recent epidemiological findings that lifetime psilocybin use was associated with significantly reduced odds of past month psychological distress and suicidality (Hendricks et al., 2015).

An innovative feature of the study design was that participants and staff monitors were given instructions that obscured the actual psilocybin dose conditions to facilitate blinding and minimize expectancy effects, which are believed to be a significant determinant of classic hallucinogen effects (Griffiths et al., 2006; Metzner et al., 1965). Evidence of some success of this blinding was provided in a post-study questionnaire completed by staff and by significant treatment effects observed after Session 1 in participants who received the very low dose of psilocybin. Although it was assumed that 1 mg/70 kg would be largely pharmacologically inactive, some pharmacological activity of this dose cannot be ruled out entirely. Thus, it might have been preferable to use an even lower dose of psilocybin (e.g. 0.01 mg/70 kg) to assure pharmacological inactivity while maintaining the benefit of the instruction that psilocybin would be administered on each session. Although the low-dose comparison condition and instructions to participants and staff facilitated blinding and minimized expectancy effects, it should be noted that these experimental design features may be difficult to implement in research settings that require complete disclosure of specific study conditions or arms.

Several additional experimental limitations should be noted. Participants were crossed over to the alternative dose condition after 5 weeks. Although this allowed assessment of acute and persisting effects of psilocybin in all study participants, it precluded double-blind assessment of efficacy of the high dose of psilocybin based on across group comparisons after 5 weeks. As in previous research, the study documented enduring increases in positive changes in attitudes and mood on both the participant-rated Persisting Effects Questionnaire and on the Community Observer Questionnaire (Griffiths et al., 2006, 2011). However, neither of these measures has been independently validated. Likewise, although the finding of significant decreases in depression and anxiety symptoms on both participant-rated and clinician-rated measures is a strength, the inclusion of blinded clinician ratings would further strengthen the study. The relatively small sample (n = 51) that was highly educated and predominately White limits the generality of conclusions.

Finally, it is important to note that the overall approach of treating cancer-related psychological distress with psilocybin is limited by a variety of exclusion criteria (see online Supplementary material) and by the significant time and cost of professional support provided before, during, and after the psilocybin session. Patients may also be reluctant to participate in such an intervention because high doses of psilocybin have sometimes been associated with transient episodes of psychological distress or anxiety in patients (current study and studies in healthy volunteers, Griffiths et al., 2006, 2011).

The neuropsychopharmacological mechanisms of psilocybin therapeutic effects remain speculative (Carhart-Harris et al., 2012, 2014; Nichols, 2016; Vollenweider and Kometer, 2010). As a 5-HT_{2A} agonist, the psilocybin metabolite psilocin directly and indirectly affects various brain cortical and subcortical areas and alters brain network dynamics (Carhart-Harris et al., 2012, 2014; Vollenweider and Kometer, 2010). Precisely how the enduring therapeutically relevant psilocybin effects are reflected in long-term alteration of cortical networks or other neuroplastic changes remains to be established.

Conclusions

When administered under psychologically supportive, double-blind conditions, a single dose of psilocybin produced substantial and enduring decreases in depressed mood and anxiety along with increases in quality of life and decreases in death anxiety in patients with a life-threatening cancer diagnosis. Ratings by patients themselves, clinicians, and community observers suggested these effects endured at least 6 months. The overall rate of clinical response at 6 months on clinician-rated depression and anxiety was 78% and 83%, respectively. A multisite study in a larger and more diverse patient population should be conducted to establish the generality and safety of psilocybin treatment of psychological distress associated with life-threatening cancer.

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References

Arrieta O, Angulo LP, Nunez-Valencia C, et al. (2013) Association of depression and anxiety on quality of life, treatment adherence, and prognosis in patients with advanced non-small cell lung cancer. *Ann Surg Oncol* 20: 1941–1948.

Barrett FS, Johnson MW and Griffiths RR (2015) Validation of the revised Mystical Experience Questionnaire in experimental sessions with psilocybin. *J Psychopharmacol* 29: 1182–1190.

Beck AT and Steer RA (1987) *BDI Beck Depression Inventory Manual*. San Antonio, San Diego, Orlando, New York, Chicago, Toronto: The Psychological Corporation Harcourt Brace Jovanovich, Inc.

Benson PL, Donahue MJ and Erickson JA (1993) The Faith Maturity Scale: Conceptualization, measurement, and empirical validation. *Res Soc Sci Stud Religion* 5: 1–26.

Breitbart W, Rosenfeld B, Pessin H, et al. (2015) Meaning-centered group psychotherapy: An effective intervention for improving psychological well-being in patients with advanced cancer. *J Clin Oncol* 33: 749–754.

Carhart-Harris RL, Bolstridge M, Rucker J, et al. (2016) Psilocybin with psychological support for treatment-resistant depression: An open-label feasibility study. *Lancet Psychiatry* 3: 619–627.

Carhart-Harris RL, Leech R, Hellyer PJ, et al. (2014) The entropic brain: A theory of conscious states informed by neuroimaging research with psychedelic drugs. *Front Human Neurosci* 8(20): 1–22.

Carhart-Harris RL, Erritzoe D, Williams T, et al. (2012) Neural correlates of the psychedelic state as determined by fMRI studies with psilocybin. *Proc Natl Acad Sci U S A* 109: 2138-2143.

Cohen SR, Mount BM, Strobel MG, et al. (1995) The McGill Quality of Life Questionnaire: A measure of quality of life appropriate for people with advanced disease. A preliminary study of validity and acceptability. *Palliat Med* 9: 207–219.

Colleoni M, Mandala M, Peruzzotti G, et al. (2000) Depression and degree of acceptance of adjuvant cytotoxic drugs. *Lancet* 356: 1326–1327.

Derogatis LR (1992) *BSI Brief Symptom Inventory: Administration, Scoring, and Procedures Manual*. Minneapolis, MN: National Computer Systems, Inc.

Dittrich A (1998) The standardized psychometric assessment of altered states of consciousness (ASCs) in humans. *Pharmacopsychiatry* 31(Suppl 2): 80–84.

Faller H, Schuler M, Richard M, et al. (2013) Effects of psycho-oncologic interventions on emotional distress and quality of life in adult patients with cancer: Systematic review and meta-analysis. *J Clin Oncol* 31: 782–793.

Gao K, Wu R, Kemp DE, et al. (2014) Efficacy and safety of quetiapine-XR as monotherapy or adjunctive therapy to a mood stabilizer in acute bipolar depression with generalized anxiety disorder and other comorbidities: A randomized, placebo-controlled trial. *J Clin Psychiatry* 75: 1062–1068.

Garcia-Romeu A, Griffiths RR and Johnson MW (2014) Psilocybin-occasioned mystical experiences in the treatment of tobacco addiction. *Curr Drug Abuse Rev* 7: 157–164.

Gasser P, Holstein D, Michel Y, et al. (2014) Safety and efficacy of lysergic acid diethylamide-assisted psychotherapy for anxiety associated with life-threatening diseases. *Journal Nerv Ment Dis* 202: 513–520.

Grassi L, Caruso R, Hammelef K, et al. (2014) Efficacy and safety of pharmacotherapy in cancer-related psychiatric disorders across the trajectory of cancer care: A review. *Int Rev Psychiatry* 26: 44–62.

Griffiths R, Richards W, Johnson M, et al. (2008) Mystical-type experiences occasioned by psilocybin mediate the attribution of personal meaning and spiritual significance 14 months later. *J Psychopharmacol* 22: 621–632.

Griffiths RR, Richards WA, McCann U, et al. (2006) Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. *Psychopharmacology* 187: 268–283.

Griffiths RR, Johnson MW, Richards WA, et al. (2011) Psilocybin occasioned mystical-type experiences: Immediate and persisting dose-related effects. *Psychopharmacology* 218: 649–665.

Grob CS, Danforth AL, Chopra GS, et al. (2011) Pilot study of psilocybin treatment for anxiety in patients with advanced-stage cancer. *Arch Gen Psychiatry* 68: 71–78.

Grof S, Goodman LE, Richards WA, et al. (1973) LSD-assisted psychotherapy in patients with terminal cancer. *Int Pharmacopsychiatry* 8: 129–144.

Halberstadt AL (2015) Recent advances in the neuropsychopharmacology of serotonergic hallucinogens. *Behav Brain Res* 277: 99–120.

Hayes AF (2013) *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach*. Guildford Press, New York.

Hendricks PS, Johnson MW and Griffiths RR (2015) Psilocybin, psychological distress, and suicidality. *J Psychopharmacol* 29: 1041–1043.

Holland JC, Andersen B, Breitbart WS, et al. (2013) Distress management. *J Natl Comp Cancer Network: JNCCN* 11: 190–209.

Hood RW Jr, Hill PC and Spilka B (2009) *The Psychology of Religion: An Empirical Approach*. New York: The Guilford Press.

Hood RW Jr, Ghorbani N, Watson PJ, et al. (2001) Dimensions of the mysticism scale: Confirming the three-factor structure in the United States and Iran. *J Sci Study Relig* 40: 691–705.

ISCDD (2003) *GRID-HAMD-17 Structured Interview Guide*. San Diego, CA: International Society for CNS Drug Development.

Johnson M, Richards W and Griffiths R (2008) Human hallucinogen research: Guidelines for safety. *J Psychopharmacol* 22: 603–620.

Johnson MW, Sewell RA and Griffiths RR (2012) Psilocybin dose-dependently causes delayed, transient headaches in healthy volunteers. *Drug Alcohol Depend* 123: 132–140.

Kast E (1967) Attenuation of anticipation: A therapeutic use of lysergic acid diethylamide. *Psychiatr Q* 41: 646–657.

MacLean KA, Leoutsakos JM, Johnson MW, et al. (2012) Factor analysis of the Mystical Experience Questionnaire: A study of experiences occasioned by the hallucinogen psilocybin. *J Sci Stud Relig* 51: 721–737.

Matza LS, Morlock R, Sexton C, et al. (2010) Identifying HAM-A cutoffs for mild, moderate, and severe generalized anxiety disorder. *Int J Methods Psychiatr Res* 19: 223–232.

McIntosh DN (1999) Purpose in Life Test (Crumbaugh & Maholick, 1964). In: Hill PC and Hood RW (eds) *Measures of Religiosity*. Birmingham, AL: Religious Education Press, pp.503–508.

McNair DM, Lorr M and Droppleman LF (1992) *Profile of Mood States*. San Diego, CA: edITS/Educational and Industrial Testing Service.

Metzner R, Litwin G and Weil G (1965) The relation of expectation and mood to psilocybin reactions: A questionnaire study. *Psychedelic Rev* 5: 3–39.

Mitchell AJ, Chan M, Bhatti H, et al. (2011) Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: A meta-analysis of 94 interview-based studies. *Lancet Oncol* 12: 160–174.

Nichols DE (2016) Psychedelics. *Pharmacol Rev* 68: 264–355.

Ostuzzi G, Matcham F, Dauchy S, et al. (2015) Antidepressants for the treatment of depression in people with cancer. *Cochrane Database Syst Rev* 6: CD011006.

Pargament KI, Koenig HG, Tarakeshwar N, et al. (2004) Religious coping methods as predictors of psychological, physical and spiritual outcomes among medically ill elderly patients: A two-year longitudinal study. *J Health Psychol* 9: 713–730.

Peterman AH, Fitchett G, Brady MJ, et al. (2002) Measuring spiritual well-being in people with cancer: The functional assessment of chronic illness therapy – Spiritual Well-being Scale (FACIT-Sp). *Ann Behav Med* 24: 49–58.

Pinquart M and Duberstein PR (2010) Depression and cancer mortality: A meta-analysis. *Psychol Med* 40: 1797–1810.

Prieto JM, Blanch J, Atala J, et al. (2002) Psychiatric morbidity and impact on hospital length of stay among hematologic cancer patients receiving stem-cell transplantation. *J Clin Oncol* 20: 1907–1917.

Reker GT (1992) *The Life Attitude Profile-Revised (LAP-R)*. Peterborough, ON: Student Psychologists Press.

Richards WA, Rhead JC, DiLeo FB, et al, (1977) The peak experience variable in DPT-assisted psychotherapy with cancer patients. *J Psychedelic Drugs* 9: 1–10.

Scheier MF and Carver CS (1985) Optimism, coping, and health: assessment and implications of generalized outcome expectancies. *Health Psychol* 4: 219–247.

Shear MK, Vander Bilt J, Rucci P, et al. (2001) Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depress Anxiety* 13: 166–178.

Shim EJ and Park JH (2012) Suicidality and its associated factors in cancer patients: Results of a multi-center study in Korea. *Int J Psychiatry Med* 43: 381–403.

Skarstein J, Aass N, Fossa SD, et al. (2000) Anxiety and depression in cancer patients: Relation between the Hospital Anxiety and Depression Scale and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire. *J Psychosom Res* 49: 27–34.

Spiegel D (2015) Existential psychotherapy for patients with advanced cancer: Facing the future and the past. *J Clin Oncol* 33: 2713–2714.

Spielberger CD (1983) *Manual for the State-Trait Anxiety Inventory*. Palo Alto, CA: Consulting Psychologists Press, Inc.

Strassman RJ, Qualls CR, Uhlenhuth EH, et al. (1994) Dose-response study of N,N-dimethyltryptamine in humans. II. Subjective effects and preliminary results of a new rating scale. *Arch Gen Psychiatry* 51: 98–108.

Studerus E, Kometer M, Hasler F, et al. (2011) Acute, subacute and long-term subjective effects of psilocybin in healthy humans: A pooled analysis of experimental studies. *J Psychopharmacol* 25: 1434–1452.

VandeCreek L (1999) The Death Transcendence Scale (Hood & Morris, 1983). In: Hill PC and Hood RW (eds) *Measures of Religiosity*. Birmingham, AL: Religious Education Press, pp.442–445.

Vollenweider FX and Kometer M (2010) The neurobiology of psychedelic drugs: Implications for the treatment of mood disorders. *Nat Rev Neurosci* 11: 642–651.

Walker J, Sawhney A, Hansen CH, et al. (2014) Treatment of depression in adults with cancer: A systematic review of randomized controlled trials. *Psychol Med* 44: 897–907.

Zigmond AS and Snaith RP (1983) The hospital anxiety and depression scale. *Acta Psychiatr Scand* 67: 361–370.

Why dying patients are suing for access to magic mushrooms

3/10/21 Jenna Greene's Legal Action 20:56:07 • Copyright (c) 2021 Thomson Reuters • Jenna Greene

Jenna Greene's Legal Action • March 10, 2021

(Reuters) - Erinn Baldeschwiler has stage 4 metastatic breast cancer. The 49-year-old mother of two teenagers was diagnosed a year ago and given two years to live.

When she spoke on Tuesday at a press conference via Zoom as a plaintiff in a pending lawsuit, she started to cry. Her son's birthday was the day before, and "I don't know how many more I'll be here for," she said. "It's just really hard."

It was a raw and devastating moment in what's usually a tightly scripted format.

But there's something Baldeschwiler thinks might help combat her overwhelming sadness and anxiety: psilocybin. And she's the face of a first-of-its-kind legal challenge to get it.

I admit, I was initially skeptical when I read the lawsuit description. Because c'mon, psilocybin? As in magic mushrooms and Grateful Dead concerts and glassy-eyed kids tripping in San Francisco's Haight-Ashbury district?

But Kathryn Tucker, special counsel at Emerge Law Group in Portland, Oregon, along with co-counsel from Perkins Coie and Yetter Coleman, argue that medical research shows that even a single therapist-guided treatment with psilocybin can provide tremendous benefits to terminal cancer patients struggling with depression and anxiety stemming from their illnesses.

For example, in a study on anxiety in terminally ill cancer patients published in the Journal of Pain and Symptom Management, one patient reported that during psilocybin therapy "I felt like I was being shown what happens after (death), like an afterlife."

"I'm not a religious person and I'd be hard pushed to say I'm anything near spiritual," the person continued, "but I felt like I experienced some of that, and experienced the feeling of an afterlife, like a preview almost, and I felt totally calm, totally relaxed, totally at peace. So that when that time comes for me, I will have no fear of it at all."

As a Schedule 1 drug, however, psilocybin remains off-limits despite recently enacted federal and state "right to try" laws intended to allow dying patients access to drugs still in investigational stages.

People like Baldeschwiler "don't have the luxury of time to wait for the very long new drug approval process," Tucker said, noting that an FDA-approved phase 1 clinical trial for psilocybin has been successfully completed, and that research continues.

Now, Tucker is leading the charge in novel litigation against the U.S. Drug Enforcement Administration after the agency refused to greenlight the therapeutic use of psilocybin for Baldeschwiler and other patients.

On March 8, the team filed a petition for review of the DEA actions before the 9th Circuit U.S. Court of Appeals, alleging that the agency's denial was arbitrary and capricious. (Under 21 U.S.C. § 877, final DEA actions are directly reviewable by courts of appeal.)

My column yesterday was also about end-of-life care, profiling Morgan, Lewis & Bockius trusts and estates partner Sara Wells, who is a hospice volunteer. Don't worry, it's not my new beat. But it does underscore how lawyers are in a unique position to help people in their lives – and their deaths.

Tucker has gained prominence over the past three decades as an advocate for patients' rights, serving as founder and director of the End of Life Liberty Project, which advocates for the rights of terminally ill patients, including for aid in dying. A 1985 Georgetown University Law Center graduate, she also previously served as executive director of the Disability Rights Legal Center.

At 14-lawyer Emerge, she co-chairs the psychedelics practice group.

The notion of a psychedelics group might sound funny, but then again, isn't that what many of us thought when firms first started forming cannabis groups about seven years ago?

Now Big Law stalwarts including Duane Morris, Seyfarth Shaw, Akerman, Fox Rothschild, Sheppard Mullin, Dorsey & Whitney, Goodwin Procter, Arent Fox and Foley Hoag all have cannabis practices.

Could medical use of psilocybin open the door wider to legalization, much like medical use of marijuana seemed to pave the wave for recreational use?

In November, Oregon voters approved Measure 109, which legalizes psilocybin for use in therapeutic settings. The measure was drafted by Emerge lawyers led by shareholder Dave Kopilak. However, it will take at least two years to implement, and (unlike cannabis) the drug will not be available for people to purchase and take home. It can only be used in a supervised therapy session.

No matter. The DEA defends its zero-tolerance stance on psilocybin.

The drug "remains a Schedule I substance under the Controlled Substances Act, meaning it has a high potential for abuse and is currently not approved for medical use in the United States," DEA public affairs specialist Amanda Purdum wrote to me in an email.

"DEA relies on and continues to support legitimate scientific research for medical treatments," she continued. "When research demonstrates that a drug is both safe and effective, and the FDA recognizes it as a legitimate treatment, DEA will take the appropriate actions."

But in the meantime, Baldeschwiler is suffering and believes psilocybin could help – or at least is worth a try.

"Whatever time I have left," she said, "I want to have the highest quality of life."

Opinions expressed here are those of the author. Reuters News, under the Trust Principles, is committed to integrity, independence and freedom from bias.

References

ARENT FOX; AKERMAN LLP; DORSEY AND WHITNEY LLP; DUANE MORRIS LLP; FOLEY HOAG LLP; MORGAN LEWIS AND BOCKIUS LLP; PERKINS COIE LLP; SEYFARTH SHAW LLP; UNIVERSITY OF SOUTHERN CALIFORNIA

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DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

Office of the Assistant Secretary
for Health
Washington DC 20201

JAN 31 1992

TO: The Secretary
Through: DS _____
COS _____
ES _____

FROM: Assistant Secretary for Health

SUBJECT: Therapeutic Use of Marijuana--DECISION

PURPOSE

On June 21, I informed you that additional marijuana would no longer be provided by PHS for new single-patient INDs. [redacted]

BACKGROUND

Marijuana is the most widely abused illicit drug in the United States. It is a psycho-active drug which impairs the mental and physical abilities of the user. The acute effects of marijuana include short term physiological changes, and cognitive and psychomotor effects.

In most marijuana users, driving performance is impaired, with frequent misjudgment of speed and longer time required for braking (1). In a study at a shock-trauma unit in Maryland, 35 percent of patients had positive blood tests for marijuana (2).

In addition, chronic users of marijuana report many of the same health problems as cigarette smokers: an increased frequency of bronchitis, emphysema, and bronchial asthma. The ability of alveolar macrophage to inactivate bacteria in the lung is also impaired. Local irritation and narrowing of the airways also

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contribute to the problems of these patients (1). Marijuana cigarettes produce proportionately more tar and benzopyrene than tobacco cigarettes (3). Also, there are many other carcinogenic hydrocarbons in marijuana smoke that have been linked with cancer development in animals (4,5).

All of the effects of THC, the main active ingredient in marijuana, on fetal development are not known. Controlled studies of over 1200 mothers revealed decreases in birth weight and length in infants whose mothers had positive urine assays for marijuana (6).

The use of marijuana by AIDS patients raises particular concerns because smoking marijuana could be highly noxious to HIV-infected patients who have compromised immune systems and are prone to pneumonia and other lung infections. Recent evidence indicates that cigarette smoking may cause the CD4 count in HIV positive individuals to fall faster (7). Additionally, marijuana smoking by AIDS patients may lead to an increased frequency in "unsafe sex" practices.

PHS Involvement in Therapeutic Study of Marijuana

In response to anecdotal claims in the 1970's that smoked marijuana relieved the nausea and vomiting accompanying cancer chemotherapy, the National Cancer Institute, under the auspices of its drug development program and in collaboration with the National Institute on Drug Abuse (NIDA), initiated clinical trials with a synthetic form of THC which is taken orally. This trial was preceded by a very small clinical study of smoked marijuana. Although the evaluations of both THC and marijuana found them efficacious, PHS chose to proceed with the development of THC because standard chemical analyses could be performed and drug administrations could be controlled. FDA approved synthetic THC marketed under the trade name Marinol for nausea associated with cancer chemotherapy in 1985.

Other anecdotal claims that marijuana or its derivative (oral THC) had therapeutic benefits for patients suffering from glaucoma (to reduce intraocular pressure) and multiple sclerosis (to reduce spasticity) were investigated with studies supported by NIH research funds. The studies suggest that both smoked marijuana and oral THC were found to be effective. Other efficacious drugs have become available, however, for the treatment of cancer, glaucoma, and multiple sclerosis.

Recently patients with HIV wasting syndrome have claimed that marijuana increases their appetite. Currently there is no drug commercially available for the treatment of this condition. There are some promising research findings from recent clinical

trials of alternatives to smoked marijuana for HIV wasting syndrome, however. Several small clinical studies of Megace indicate some efficacy for the treatment of anorexia and weight loss in AIDS patients (8,9). Megace is the trade name for Megestrol acetate which is a synthetic hormone which has indicated uses in the treatment of advanced ovarian and breast cancers. Clinical trials of Marinol for treatment of HIV wasting syndrome are underway in eight cities. The dose being studied produces little if any intoxication. PHS has reviewed the merits of undertaking additional research studies of smoked marijuana and determined that it is not a priority at this time.

The FDA IND Process

Physicians of seriously ill patients can apply to use unapproved drugs through FDA's investigational new drug (IND) program. To file for an IND, FDA requires the physician to document the patient's medical history; submit a protocol for use of the drug; provide a summary of the conventional therapies tried; develop an individual treatment plan; and provide a letter from the drug supplier to the physician confirming the availability of the drug for this purpose. In the case of marijuana where the Federal Government is the only supplier, under current procedures NIDA must certify that the drug is available. After certification of availability NIDA informs the applicant that shipments can begin after the receipt of a NIDA prepared disclaimer form and a copy of the physician's DEA registration. DEA must register all physicians who prescribe Schedule I drugs. DEA's approval is contingent upon a site inspection which reviews security and a criminal background investigation.

Approved applicants are also required to file an annual report documenting the effect of the drug on the patient's illness and include a statement as to whether the patient should continue with the experimental therapy as originally requested.

Legal Authority

OGC has reviewed NIDA's authority and has determined that it is limited to supplying marijuana for scientific research purposes only. Currently, NIDA is the only legal source of marijuana. In fact, international treaties prohibit entities other than the Federal Government from legally supplying marijuana.

The Department, through the IND process, began providing marijuana in 1978 to one patient under an agreement in settlement of a lawsuit against the Government. As far as can be determined from available court papers, the settlement involved only the one individual and actually only obligated the Government for two years. Nevertheless, we have continued to supply that individual through the present time. Also, marijuana has been supplied to a

few others through the same mechanism. However, until 1989 the number of applications for marijuana was quite small. Since 1989 the number of applications has increased from approximately 3 to a high of 46.

Currently, 13 persons are actually receiving marijuana. Twenty-eight applications are pending. (Pending applications are those which have been accepted by FDA and NIDA but shipments of marijuana have not begun.) None of the pending applicants have provided the appropriate documentation (disclaimer and DEA registration form) to become eligible to receive shipments. A list of active and pending applications and the illnesses for which they are requested is attached.

[redacted]

Twenty-six additional applications have been received since PHS began examining its policy which are not included in the pending category.

DISCUSSION

Subsequent to forwarding the June 21 memorandum to you, PHS components (as well as ONDCP) considered several issues related to implementing that policy. Those issues included the pros and cons of allowing some patients to receive the drug while denying others, the handling of new single-patient IND requests, and the feasibility of studies using oral THC (Marinol).

I reviewed these issues thoroughly with relevant Agency Heads and appropriate members of OASH Senior Staff.

[redacted]

1

2

3. [redacted]

OPTIONS

Option 1: Immediately cease shipment of marijuana to all patients currently receiving the drug through the single-patient IND mechanism.

Pros:

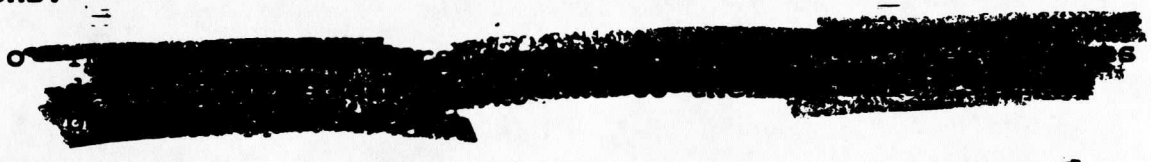
- [redacted]
- [redacted]
- [redacted]

Cons:

Option 2: Continue shipment of marijuana only to the patients with active applications (13) for an indeterminate period while patients and their physicians are aided and encouraged to explore existing alternative therapies. This would, in effect, extricate PHS from supplying marijuana through single-patient INDs by attrition. While PHS would not begin shipping to those with pending applications, PHS would work with all physicians with pending applications to inform them of alternative therapies.

Pros:

Cons:



o [redacted]

Option 3: Continue shipment of marijuana to all active patients and begin shipment to all patients with pending applications (a total of 41 persons) for an indeterminate period. As patients drop out, no new patients would be added. Although marijuana will be available for these patients, PHS will work with all physicians with pending applications to aid and encourage them to try alternative therapies for their patients.

Pros:

o [redacted]

o [redacted]

o [redacted]

Cons:

o [redacted]

o [redacted]

o [redacted]

o [redacted]

RECOMMENDATION:

PHS recommends option 2.

DECISION:

1. Option: Immediately cease shipment of marijuana to all patients currently receiving the drug through the single-patient IND mechanism.

   Approve _____ Disapprove _____ Date _____

2. Option: Continue shipment of marijuana to all patients (13) with active applications for an indeterminate period while patients and their physicians would be aided and encouraged to explore existing alternative therapies. PHS would not begin shipping to those with pending applications.

   Approve _____ Disapprove _____ Date 3-4-92

3. Option: Continue shipment of marijuana to all active patients and begin shipment to all patients with pending applications (a total of 41 persons) for an indeterminate period.

   Approve _____ Disapprove _____ Date _____

James O. Mason

James O. Mason, M.D., Dr.P.H.

Attachment

REFERENCES

1. Mirin, S.M. and Weiss, R.D. Substance Abuse. In Bassuk, E.L., Schoonover, S.C. III, and Gelenberg, A.J., eds. The Practitioner's Guide to Psychoactive Drugs. New York: Plenum Publishing Corp., 221-282, 1983.

2. Soderstrom, C.A., Trifillis, A.L., Shankar, B.S., Clark, W.E., and Cowley, R.A. Marijuana and alcohol use among 1023 trauma patients. Archives of Surgery, 123, 733-768, 1989.

3. Novotny, M., Lee, M.L., and Bartle, K.D. A possible chemical basis for the higher mutagenicity of marihuana smoke as compared to tobacco smoke. Experientia, 32, 280, 1976.

4. Cohen S., and Stillman, R.C. The Therapeutic Potential of Marijuana. New York: Plenum Press, 1976.

5. Relman, A.S. Marijuana "justifies serious concern." In Marijuana and Health. Washington: National Academy Press, 1982.

6. Zuckerman, B., Frank, D.A., Hingson, R., et al. Effects of maternal marijuana and cocaine on fetal growth. New England Journal of Medicine, 320, 762-768, 1989.

7. Plasse, T.F. Clinical use of THC: letter to the editor. J. Clinical Oncol., in press, 1991.

8. Dickmeyer, M.S., Brown, S., Pursell, K., Thaler, H., and Armstrong, D. Improved appetite and weight gain in patients with Acquired Immune Deficiency Syndrome treated with megestrol acetate. Int. Conf AIDS. June 16-21;1-231 (abst. M.B. 2198), 1991.

9. Von Roenn, J., Roth, E., Murphy, R., Weitzman, S., Armstrong, D., and the U.S. Megestrol Acetate Study Group. Controlled trial Megestrol Acetate for the treatment of AIDS related anorexia and cachexia. Int. Conf. AIDS June 16-21; 1:280(abst. W.B. 2392).

Drug Enforcement Administration

Washington, D.C. 20537

MAR 4 1992

James O. Mason, M.D.
Doctor of Public Health
Assistant Secretary for Health
Department of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Dr. Mason:

The issue of the proper Controlled Substances Act (CSA) schedule for marijuana has been contested by various groups since 1971. These groups have attempted to have the substance taken out of Schedule I and placed in a less restrictive category to do what the advocates of rescheduling refer to as "making the drug more available." The current efforts of the rescheduling advocates involve having many physicians apply to the Food and Drug Administration (FDA) for approval of single patient Investigational New Drug (IND) applications. At the same time, applications for registration are submitted to the Drug Enforcement Administration (DEA). The groups have vigorously pushed a letter writing campaign to congressmen and senators. Reviewing the many applications for registration and responding to congressional inquiries on the availability of marijuana to treat various maladies has placed a burden on staff members of this Agency. I am sure that a similar burden has been placed on staff members of the Department of Health and Human Services (DHHS).

To date, the applications for registration for the single patient studies have involved the following conditions: nausea and vomiting associated with chemotherapy, radiation therapy, brain tumor and hydrocephalus; the loss of appetite associated with AIDS or treatments for the disease; the spasticity and pain associated with multiple sclerosis, paralysis, nerve damage of various etiologies, multiple congenital cartilaginous exostosis, tendinitis, osteoarthritis, pseudo-pseudo hypoparathyroidism and a variant of the latter; increased intraocular pressure of glaucoma, and the signs or symptoms associated with the nail-patella and Ehlers Danlos syndromes.

The DEA is not aware of any evidence which indicates that any patient benefits are derived from the use of marijuana in any of the above conditions. We have taken the position that these rescheduling advocates are using the medical issue for a cause which has nothing to do with the treatment of disease. Many of

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TRACER

the advocates of rescheduling have been documented as marijuana smokers for many years and are using the suffering of people with serious medical problems as a means of making marijuana more readily available for their own use. I am sure they are well aware of the approval process of FDA but are looking for a legislative or court determination of the medical utility of marijuana.

The DEA is totally committed to the facilitation of all bona fide research with controlled substances. However, the use of marijuana in the single patient studies being pushed will not demonstrate the medical utility of the substance. Responding to congressional inquiries, applications for registration and matters related to the IND's is placing an undue burden of work on the DEA and probably DHHS as well.

In light of the above, it seems that it would be appropriate for representatives of the DHHS and the DEA to work together to formulate policies on regulatory issues related to the use of marijuana in the treatment of disease. If you agree, please have your designee contact an official of the DEA to work on the policy issues involved. I have designated Gene R. Haislip, Deputy Assistant Administrator, Office of Diversion Control, to represent this Agency in these matters. Mr. Haislip may be reached at (202) 307-7165.

I look forward to hearing from you.

Sincerely,

Stephen H. Greene

Stephen H. Greene
Acting Deputy Administrator

DEPARTMENT OF HEALTH & HUMAN SERVICES — Public Health Service

CDER / HHS - Fax Memo

Date: Thursday, April 23, 1992

To: Francesca Cook ,
phone 472-3033 , fax 245-6608

cc: John Harter, Corinne Moody, Michael Klein

From: Dan Spyker

Subject: Letters to IND Investigators Receiving Marijuana Out

---

There follows a *Letter List* including all investigators currently receiving marijuana. A letter was prepared and signed 4/15/92 for each of these physicians . Then follows a copy of one of the letters. → Francesca, Here's a copy of one of the letters, I forgot to include the list the first time. Dalene

Let me know if you have any comments or questions.

If you responded to [redacted] I would be interested in receiving a copy of your response.

Thank you for your help with this difficult matter.

- dan

..... end of message .....

Sent by Dalene Time 3:00

phone 301-443-3741, fax 301-443-7068

Center for Drug Evaluation and Research
Pilot Drug Evaluation Staff
Room 9B-45 Parklawn Building
HFD-007, 5600 Fishers Lane
Rockville, MD 20857

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

[redacted]

[redacted]

Dear

Based upon concern regarding the provision of a potentially harmful substance to patients as medicine, marijuana cigarettes will no longer be available to those not currently receiving them through the single-patient IND program. While shipments to your patient will continue as before, we thought it was important for you to understand the reasons behind the Department's decision to terminate the program.

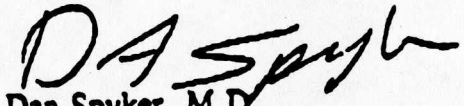
Clinically, marijuana has many drawbacks as a medicine. Marijuana is not a pure drug and may be contaminated with pathogens. Smoked marijuana delivers irritants that could be highly noxious to patients with chronic illness or immunosuppression. In addition, after reviewing the available data, scientists at the National Institutes of Health (NIH) have concluded that existing evidence does not support recommending smoked marijuana as the treatment of choice for any medical condition. Further, there are effective and safer alternatives available for all illnesses for which marijuana is being requested.

As you may know, tetrahydrocannabinol (THC), the principal active ingredient in marijuana is available as an oral prescription drug, dronabinol (Marinol). Clinical trials of Marinol treatment for HIV wasting syndrome are almost completed and NIH is beginning a study of Marinol in combination with megestrol (Megace) for this problem.

Although marijuana cigarettes are still available to your patient we are interested in working with you to explore alternative methods of managing your patient's illness. We have identified an expert at NIH who is experienced in the management of glaucoma and he/she would be happy to contact you to discuss with you current research protocols and specific management approaches.

In our decision-making process, we sought to find a balance between providing everything possible to ease the suffering of chronically ill patients while at the same time adhering to best medical practice. We also had to bear in mind that under existing Public Health Service (PHS) legislation, we have authority to provide marijuana only for research. Please contact Corinne Moody, the Consumer Safety Officer, or me at 301-443-3741 if you would like to speak with the NIH contact or if you have any questions.

Sincerely,



Dan Spyker, M.D.
Medical Officer
Pilot Drug Evaluation Staff
Center for Drug Evaluation and Research

The Controlled Substances Act

by William W. Vodra
Office of the General Counsel
Department of Health, Education, and Welfare

The raison d'être of the Controlled Substances Act (CSA) is to enable the U.S. Government to minimize the quantity of drugs of abuse which are available to persons who are prone to abuse drugs. The Controlled Substances Act is precisely that—an act to control certain substances.

This paper summarizes three fundamental and important parts of the Act: (1) the effects of controlling a substance under the Act; (2) the procedures for bringing a substance under the controls of the Act; and (3) the criteria for determining whether a substance should be controlled.

I. The Control Mechanisms

Two agencies share responsibility for enforcing the controls of the Act: the Food and Drug Administration (FDA) in the Department of Health, Education, and Welfare and the Drug Enforcement Administration (DEA) in the Department of Justice.

There are nine control mechanisms imposed on the manufacturing, obtaining, and selling of substances listed under the Controlled Substances Act. These are: (1) Registration of handlers; (2) Recordkeeping requirements; (3) Quotas on manufacturing; (4) Restrictions on distribution; (5) Restriction on dispensing; (6) Limitations on imports and exports; (7) Conditions for storage of drugs; (8) Reports of transactions to the government; and (9) Criminal penalties for illicit trafficking. The first two controls are equally applicable to substances listed in every schedule; the others vary, depending upon the schedule involved.*

* There is a third requirement applicable to all controlled substances which relates to the labeling of the containers in which they are kept. A special symbol in the form of a C plus the roman numeral for the number of the schedule in which the drug is placed (e.g., C-III) must appear on the label and upon the labeling. This is not, in fact, a control mechanism. It serves instead to inform the pharmacist and the physician (the only ones to see the label and labeling in most circumstances) that the drug which they are handling is a controlled substance and is subject to special restrictions regarding handling and recordkeeping. (See Section 305 of the Act.)

William W. Vodra was formerly Assistant Chief Counsel of the Drug Enforcement Administration. He was the principal author of DEA's regulations and was largely responsible for developing the theory and philosophy of our quota system. Mr. Vodra's transfer to the Department of Health, Education, and Welfare to work with the Food and Drug Administration represented both a loss and a gain for DEA. We lost a fine lawyer. In having at FDA a man acutely aware of DEA's problems and responsibilities, we gained a greater ability for cooperation between the two agencies. That cooperation is essential if the Congressional intent in enacting the Controlled Substances Act is to be realized.

I have read Mr. Vodra's article and, were I his editor, might quibble over a very few small points. But I am not. This is Mr. Vodra's work and I commend it to the reader.

Robert J. Rosthal
Deputy Chief Counsel
Drug Enforcement Administration

Registration

Every person who desires to handle a controlled substance must be registered with DEA. A unique number is assigned to each legitimate handler of controlled drugs: importer, manufacturer, wholesaler, hospital, pharmacy, physician, and researcher. This number is readily available to suppliers who wish to verify the authenticity of a potential customer. Thus the opportunity for unauthorized transactions is greatly diminished. The registration system also provides a means of expeditiously excluding persons who have been found participating, consciously or unconsciously, in the diversion of drugs.

In the past a company was relatively immune from sanction for failing to take adequate steps to prevent diversion. A lengthy trial was needed to establish the offense, and generally only a monetary fine would result. It was cheaper for a handler to risk paying a fine than to put in the necessary security controls which would prevent diversion. Today, a relatively speedy administrative hearing can establish inadequate security, and the penalty is loss of registration. The handler now risks being put out of business; it has become cheaper to provide precautions against diversion. (See Sections 301-304 of the Act.)

Recordkeeping

The other control mechanism applicable to all substances under control, regardless of the schedule in which they are placed, is the requirement that full records be kept of all manufacturing, purchases, sales, and inventories of the substance by each handler. There are limited exemptions from this requirement available to physicians and to researchers.

From these records it is possible to trace the flow of any drug from the time it is first imported or manufactured through the wholesale level, to the pharmacy or hospital that dispensed it, and then to the actual patient who received the drug. The mere existence of this requirement is sufficient to discourage many forms of diversion; it actually serves large corporations as an internal check to uncover diversion such as pilferage by employees.

There is one distinction between scheduled items for recordkeeping requirements. Records for Schedule I and II drugs must be kept separate from all other records of the handler; records for Schedule III, IV, and V substances must be kept in a "readily retrievable" form. The former method allows for more expeditious audits, but does increase the cost of recordkeeping to the handler. (See Section 307 of the Act.)

Quotas

DEA, working jointly with FDA, limits the quantity of controlled substances listed in Schedules I and II which can be produced during any given calendar year.* There is probably more misunderstanding about quotas than any other control mechanism imposed under the CSA.

The methodology for setting quotas is still in its infancy. Until recently, the Federal Government was dependent upon the data furnished by the bulk manufacturers of the substances subject to quota. Today, we have access to special reports filed by all manufacturers and distributors of controlled drugs, information derived from commercial prescription surveys, data from triplicate prescription programs operated in four states, reports from insurance carriers regarding prescription reimbursement, and special surveys regarding the quantities of drugs dispensed directly by physicians and the quantities used in hospitals. As a result the Government has far more data than ever before with which to project actual drug usage.

There remains an unresolved problem, however, of whether quotas can be set in such a way that they will have a direct impact upon diversion. There is no obvious relationship between limitations on the quantities of drugs produced and the quantities of drugs diverted by fraud, theft, or negligence to illicit channels. At the present time quotas work best when they are applied to cut gross overproduction of drugs by manufacturers and when they are used to reduce the number of handlers in the marketplace by eliminating the marginal manufacturers.† Two negative aspects of quotas can be increased prices to the consumer because of decreased competition, particularly by small generic manufacturers, and insufficient supplies for bona fide medical practice because of overly conservative estimates of medical needs. (See Section 306 of the Act.)

* Although the statute speaks exclusively in terms of Schedules I and II, it should be noted that certain drugs in Schedules III and V derive from materials which are listed in Schedule II; codeine syrups, for example, are made by combining codeine, a Schedule II drug, with other ingredients in a special diluted form. Therefore most narcotic drugs in Schedules III and V, as well as certain amphetamine and barbiturate combination drugs in Schedule III, are in fact subject to quota as well.

† When the first amphetamine quotas were established in 1972, the number of amphetamine manufacturers was estimated at approximately 100; today there are fewer than 40, the remaining 60 having found that the quantity allocated to them under the quota system was insufficient to make it profitable to remain in the business.

Distributions

All distributions of a controlled substance—from one manufacturer to another, from manufacturer to wholesaler, from importer to wholesaler, and from wholesaler to dispenser—are restricted. In the case of Schedule I and II drugs, the supplier must have a special order form from the customer. This order form is issued by DEA only to persons who are properly in Schedules I and II. The form is preprinted with the name and address of the customer. The drugs must be shipped to this name and address; any change in the form renders it invalid. The use of this device is a special reinforcement of the registration requirement; it makes doubly certain that only authorized individuals may obtain Schedule I and II drugs. Another benefit of the form is a special monitoring it permits. The form is issued in triplicate: the customer must keep one copy for his own files; he forwards two copies to the supplier who, after filling the order, keeps a copy for his own records and forwards the third copy to Federal agents for review. (See Section 308 of the Act.)

For drugs in Schedules III, IV, and V, no order form is necessary. The supplier in each case, however, is under an obligation to verify the authenticity of his customer by checking the registration number used by the customer against the official files which are available at DEA. The supplier is held fully accountable for any drugs which are shipped to a purchaser who does not have a valid registration.

Dispensing to Patients

The dispensing of a controlled substance is the delivery of the controlled substance to the ultimate user, who may be a patient or research subject. Special control mechanisms operate here as well. Schedule I drugs are those which have no currently accepted medical use in treatment in the United States; they may therefore be used only in research situations. They generally are supplied by only a limited number of manufacturers directly to authorized researchers who administer them directly to the subjects.

For most (if not all) Schedule II, III, and IV drugs, a prescription is required under the Federal Food, Drug, and Cosmetic Act. The determination to place drugs on prescription is within the jurisdiction of FDA. Unlike other prescription drugs, however, these are subject to additional special restrictions. Schedule II prescriptions must be written and signed by the practitioner; they may not be telephoned in to the pharmacy. In addition, the prescription may not be refilled; the patient must return to the physician in order to obtain more drugs. For Schedule III and IV drugs, the prescription may be either written or oral (that is, by telephone to the pharmacy). In addition, the patient may (if authorized by the doctor on the initial prescription) have the prescription refilled on his own decision up to five times and at any time within six months from the date of the initial filling.

These restrictions merely reflect an extension of the entire philosophy underlying prescription requirements generally. Some drugs can be self-administered with minimal risk to the user; these are allowed to be sold over the counter without a prescription. Other drugs pose risks which must be balanced against the benefits for each individual; because professional assistance is essential in achieving this balance, the law requires a physician's approval (in the form of a prescription) before the patient can obtain the drug. Once he has obtained the prescription, however, the patient has reasonably free access to the drug by means of refills; the physician can indicate unlimited refills if he so desires. But because some prescription drugs threaten to create dependence or to be used for non-medical purposes harmful to the patient, the CSA has required continual physician approval by limiting or forbidding refills. In effect, the Act says that when being treated with the most dangerous drugs (Schedule II), the patient should see his physician more frequently than when being treated with other drugs. Similarly, use of the other dangerous drugs (in Schedules III and IV) requires frequent physician review, although not as frequent as with Schedule II because of the lesser danger of dependence resulting.

Schedule V is currently reserved for the over-the-counter (OTC) narcotic preparations including antitussives and antidiarrheals. Even here, however, the law imposes restrictions beyond those normally required for the over-the-counter sales; for example, the patient must be at least 18 years of age, must offer some form of identification, and have his name entered into a special log maintained by the pharmacist as part of a special record. (See Section 309 of the Act.)

Import and Export

To oversimplify slightly, any international transaction involving a Schedule I or II controlled drug must have the prior permission of DEA; and any international transaction involving a Schedule III, IV, or V controlled substance must be made with prior notice

to (but without requiring prior approval of) DEA. Approval to import a Schedule I and II drug will not be given until the importer shows that there is not a sufficient domestic supply with adequate competition. Similarly, exportation of Schedule I and II drugs is severely limited and requires demonstration that the drugs are going to a country where they will actually be used and will not be re-exported from the country of destination. These restrictions tend to diminish the amount of international transactions in an area where diversion has long been known to occur.* (See Sections 1002-1003 of the Act.)

Security for Storage of Drugs

DEA prescribes the requirements for the security of premises which contain controlled substances as a condition to registration under Section 303 of the Act. In the case of Schedule I and II drugs, exceptionally high security requirements are imposed: a specially constructed vault with reinforced concrete walls and a steel gate, a 24-hour alarm system, and immediate availability of security guards, to name a few. For drugs in Schedules III, IV, and V, the vault is an optional feature. In lieu of a vault, the handler may segregate the controlled substances in a special area where they are under constant surveillance by supervisory personnel. The requirements of an alarm system and security guards are still imposed. These costly special requirements for storage apply only to manufacturers, importers, exporters, and wholesalers of controlled drugs. They do not apply to the retail handlers such as physicians, pharmacies, and hospitals; in these cases reduced security requirements are imposed to correlate with the smaller quantities of drugs involved and the special security needs of these handlers. It should also be noted that special security requirements are imposed for areas where drugs are manufactured or processed and that DEA is reviewing security requirements for shippers of controlled substances as well as for employees who have access to these drugs. (See 21 CFR 1301.71-76.)

Reports to DEA

Periodic reports regarding transactions in certain drugs must be submitted to DEA. A new program, called ARCOS, was inaugurated on January 1, 1974. This program involves monitoring all drugs listed in Schedules I and II and all narcotic drugs in Schedule III. Every 90 days, each manufacturer and wholesaler of any of these drugs must report all manufacturing activities, all importation and exportation, and all distributions to DEA; inventories must also be filed annually. These reports are processed by computer and enable the Federal Government to identify excessive purchases or discrepancies between purchases and sales not reflected in inventory on a product-by-product, handler-by-handler basis. This project will ultimately provide the most detailed information regarding production and use of controlled substances that has ever been available. (See Section 307(d) of the Act.)

Criminal Penalties for Trafficking

The most common and well-known control mechanism has not yet been mentioned: the criminal sanctions for illicit trafficking. Trafficking is defined as the unauthorized manufacture, the unauthorized distribution (i.e., delivery whether by sale, gift, or otherwise), or the possession for unauthorized manufacture or distribution of any controlled substance. The penalties for violation of this restriction are related to the schedules as well. For narcotics in Schedules I and II, a first offense is punishable by up to 15 years in prison and up to a $25,000 fine. For trafficking in a Schedule I and II nonnarcotic drug or any Schedule III drug, the penalty is up to five years in prison and up to a $15,000 fine. Trafficking in a Schedule IV drug is punishable by a maximum of three years in jail and up to a $10,000 fine. And trafficking in a Schedule V substance is a misdemeanor punishable by up to one year in prison and up to a $5,000 fine. Second and subsequent offenses are punishable by twice the penalty imposed by the first offense.

It must be emphasized that possession for one's own use of any controlled substance in any schedule is always a misdemeanor on the first offense, punishable by one year in jail and up to a $5,000 fine. The CSA very carefully distinguishes between trafficking offenses (that is, crimes by those who are supplying illicit drugs to abusers) and use offenses (that is, crimes by persons who actually use drugs themselves).

* The Single Convention on Narcotic Drugs requires restrictions similar to those imposed by the CSA.

(Text continued on page 34. A chart of CSA control mechanisms is presented on pages 6 and 7.)

Control Mechanisms of the CSA

Schedule	Registration	Recordkeeping	Manufacturing Quotas	Distribution Restrictions	Dispensing Limits
I	Required	Separate	Yes	Order forms	Research use only
II	Required	Separate	Yes	Order forms	Rx: written; no refills
III	Required	Readily retrievable	No *but* Some drugs limited by Schedule II quotas	DEA registration number	Rx: written or oral; with medical authorization, refills up to 5 times in 6 months
IV	Required	Readily retrievable	No *but* Some drugs limited by Schedule II quotas	DEA registration number	Rx: written or oral; with medical authorization, refills up to 5 times in 6 months
V	Required	Readily retrievable	No *but* Some drugs limited by Schedule II quotas	DEA registration number	OTC (Rx drugs limited to MD's order)

This chart summarizes the control mechanism in a format which permits comparison between the schedules in terms of the controls imposed.

Note that the distinction between Schedule III and Schedule IV is virtually nonexistent. Other than the penalties for criminal trafficking, the statute makes no distinction whatsoever. DEA, in imposing regulatory controls, has singled out narcotic drugs in Schedule III for coverage under the ARCOS system. By indirect means, some narcotics and non-narcotics in Schedule III are also under the quota system.

The differences between Schedule V and Schedules III and IV are also very small. The only practical distinction is that Schedule V drugs are generally over-the-counter, a differentiation imposed not by the CSA but by FDA in determining which drugs

Import-Export		Security	Manufacturer/ Distributor Reports to DEA	Criminal Penalties for Trafficking (First Offense)	
Narcotic	**Non-narcotic**			**Narcotic**	**Non-narcotic**
Permit	Permit	Vault type	Yes	15 years/ $25,000	5 years/ $15,000
Permit	Permit	Vault type	Yes	15 years/ $25,000	5 years/ $15,000
Permit	Notice	Surveillance	Yes Narcotic	5 years/ $15,000	5 years/ $15,000
			No Non-narcotic		
Permit	Notice	Surveillance	No Narcotic	3 years/ $10,000	3 years/ $10,000
			No Non-narcotic		
Permit to import	Notice	Surveillance	Manufacturer only Narcotic	1 year/ $5,000	1 year/ $5,000
Notice to export			No Non-narcotic		

should be subject to prescription requirements.

Schedules I and II are subject to almost identical restrictions except that Schedule I drugs, since they have no medical use, can only be dispensed in research circumstances, whereas Schedule II drugs can be dispensed upon prescription in a pharmacy.

important to keep in mind when analyzing the criteria for placement of the drug in a given schedule; for while Congress devoted considerable effort toward suggesting gradations among Schedules II, III, IV, and V, it drew few distinctions in the controls to be imposed.

(Continued from page 5)

II. Procedures for Controlling Substances

The various procedures for controlling a substance under the CSA are set forth in Section 201 of the Act. Proceedings may be initiated by the Department of Health, Education, and Welfare (HEW), by DEA, or by petition from any interested person registered with DEA. An interested person could be the manufacturer of a drug, a medical society or association, a pharmacy association, a public interest group concerned with drug abuse, a state or local government agency, or an individual citizen. When a petition is received by DEA, the agency begins its own investigation of the drug. In most cases, this process has led to a report and recommendation to HEW with far more data than was contained in the original petition.

Formal Scheduling Procedure

Once DEA has collected the "necessary data," the Administrator of DEA (by authority of the Attorney General) requests from HEW a "scientific and medical evaluation" and recommendations as to whether the drug or other substance should be controlled or removed from control.* This request is filed with the Commissioner of FDA, who has the responsibility for coordination of activities within HEW.† The Commissioner solicits evaluations and recommendations from the affected bureaus within FDA (e.g., Bureau of Drugs, Bureau of Veterinary Medicine), from the National Institute of Drug Abuse, and from the Controlled Substances Advisory Committee. There is no statutory requirement that HEW receive comments from, or provide a hearing to, interested parties in preparing its evaluation and recommendations. A reason for creating this advisory committee, however, is to provide a forum whereby HEW can hear from interested persons, the medical and scientific community, and the public. Once these evaluations are received, the Commissioner submits a report and recommendations to the Assistant Secretary for Health. The Assistant Secretary (by authority of the Secretary) then transmits back to DEA his medical and scientific evaluation regarding the substance and his recommendations as to whether the drug should be controlled.

The medical and scientific evaluations are binding on DEA with respect to scientific and medical matters. The recommendation on scheduling is binding only to the extent that if HEW recommends that the substance not be controlled, DEA may not control the substance. While the issue has never been legally resolved, it is understood by DEA and HEW that DEA may not exceed the level of control recommended by HEW but may take final action for a lower level of control than that recommended. For example, if a drug is recommended by the Assistant Secretary for Health for control in Schedule III, DEA may place the drug in Schedule III, IV or V, but may not place it in Schedule II.

Once DEA has the medical and scientific evaluation and recommendation from HEW, it will proceed to make a final internal decision on whether to control the drug and, if so, in which schedule. If it is determined to control the drug, a proposal will be published in the Federal Register setting forth the schedule in which the control is proposed, summarizing the reasons for control, and inviting all interested persons to file comments with DEA. Affected parties may also request a hearing with DEA. If no hearing is requested, DEA will evaluate all comments received and publish a final order in the Federal Register, controlling the drug as proposed or with modifications based upon the written comments filed. This order will set the effective dates for imposing the various control mechanisms.

If a hearing is requested, DEA will enter into discussions with the party or parties requesting a hearing in an attempt to narrow the issues for litigation. A hearing will then be held before an Administrative Law Judge appointed by the Civil Service Commission; he will take evidence on factual issues and hear arguments on legal questions regarding the control of the drug. Depending on the scope and complexity of the issues, the hearing may be brief or quite extensive. The Administrative Law Judge, at the close of the hearing, prepares a recommended set of findings of fact and conclusions of law which are submitted to the Administrator of the Drug Enforcement Administration. The Administrator will review these documents as well as the underlying material, and prepare his own findings of fact and conclusions of law (which may or may not be the same as those drafted by the Administrative Law Judge). He then publishes a final order in the

* The word "control" includes the transfer of a drug from one schedule to another, the removal of a drug from all schedules, and the scheduling of a drug for the first time.

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Federal Register either imposing controls or declining so to do.

Once the final order is published in the Federal Register, interested parties have 30 days to appeal to a U.S. Court of Appeals to challenge the order. Findings of fact of the Administrator are deemed conclusive if supported by "substantial evidence." The order imposing controls is not stayed during the appeal, however, unless so ordered by the court.

Summary Scheduling Procedure

What has been discussed to this point has been the formal scheduling process under Sections 201(a), (b) and (c) of the Controlled Substances Act. There are, however, procedures which permit scheduling of a drug without recourse to the procedures outlined above. Under Section 201(d), when control is required by a treaty regarding drug control to which the United States is a party, the Attorney General is required to issue an order controlling the drug under the schedule he deems most appropriate to carry out the treaty obligations, without going through the formal processes of reference to HEW, receipt of recommendations and evaluations by HEW, and notice in the Federal Register with an opportunity for a hearing by affected parties.

With the exception of three drugs listed in the Convention on Psychotropic Substances, all drugs listed under the narcotics treaties and all the drugs listed under the Convention on Psychotropic Substances (to which the United States is not yet a party) are controlled under the CSA. In order for drugs to be controlled in the future under an international treaty, a vote of the Commission on Narcotic Drugs is required. The United States is a permanent member of the Commission on Narcotic Drugs. (In addition, as a prerequisite to a vote by the Commission on Narcotic Drugs, the World Health Organization is required to evaluate the drug and make recommendations; in this body the United States has a significant input on these matters.) It is now contemplated that when a question of drug control is to be presented to the Commission on Narcotic Drugs, the vote by the United States would be determined through consultation between the same agencies and basically in the same manner as normal scheduling decisions.

Secondly, if drug control is required under a treaty and the Attorney General places the drug in a schedule which he deems most appropriate to carry out the treaty obligations, interested parties who believe that another schedule could be equally appropriate are permitted to commence a drug-scheduling process through a petition to DEA to reschedule the drug in the alternate schedule. HEW may also initiate a rescheduling action. Any rescheduling proposed or petitioned, however, must be consistent with U.S. treaty obligations; the Attorney General cannot take an action which would violate the requirements under such treaties.

A summary procedure for scheduling certain substances is also provided for in Section 201(e), which permits DEA to place "immediate precursors" of a controlled substance at the same level of control as the controlled substance itself or at a lesser level of control. An immediate precursor is defined in the CSA as being a substance which is the "principal compound used or produced primarily for use in the manufacture of a controlled substance"; which is "an immediate chemical intermediary used or likely to be used in the manufacture of the controlled substance"; and the control of which "is necessary to prevent, curtail or limit the manufacture of the controlled substance." An example of this type of scheduling is the control of lysergic acid, which is the immediate precursor to lysergic acid diethylamide (LSD).

Exception Procedures

There are additional procedures for *partial* control of a controlled substance; that is, the exemption of a controlled substance from certain control mechanisms. These are of three types:

(1) Any non-narcotic substance which may be sold over-the-counter without a prescription under the Federal Food, Drug, and Cosmetic Act *cannot* be controlled. (See Section 201(g) of the Act.) This section has been interpreted to apply to over-the-counter products which contain controlled substances; for example, Primatine, a tablet containing phenobarbital and ephedrine, is excluded from control under this procedure.

(2) Chemical preparations and mixtures containing one or more controlled substances which are intended for laboratory, industrial, educational or research purposes and not for general administration to a human being or other animal, may be exempted from controls. The preparation or mixture must either contain no narcotic controlled substance and be packaged in a form or concentration such that it presents no significant potential for abuse, or contain a narcotic or non-narcotic controlled substance and also one or

more adulterating or denaturing agents in such a way that the combination does not present a potential for abuse. This exemption authority does not specifically appear in the statute but derives from inherent powers of DEA to provide for the efficient execution of the statute pursuant to Section 501(b). The exemption was adopted to eliminate unnecessary restrictions on chemical preparations which contain very small quantities of controlled substances or which were combined or treated in such a way as virtually to eliminate any potential for abuse. Among the items included in this list are buffering agents, reference standards, and reagents. To date all exemptions in this category have been handled administratively by DEA. Neither the general criteria for exemption nor any specific individual cases have been evaluated by HEW. (See 21 CFR 1308.23-24.)

(3) Non-narcotic prescription drugs listed in Schedules III, IV or V may be exempted from some control mechanisms (labeling, recordkeeping, prescription limits, and import-export restrictions) if contained in a compound, mixture, or preparation which contains one or more active medicinal ingredients not having a depressant or stimulant effect on the central nervous system and combined in such a way as to vitiate the potential for abuse of the controlled substance. The authority for this exemption is provided in Section 202(d) of the Act. Registration requirements, distribution restrictions, and penalties for criminal trafficking remain in force. Criteria for exempting drugs under the section were developed under the Drug Abuse Control Amendments of 1965, which contained language similar to the CSA. Subsequently, the National Academy of Sciences-National Research Council developed a different set of criteria for determining which combination drugs should be exempt; these criteria were never implemented because the Controlled Substances Act was then pending in Congress. The criteria by which DEA is currently operating have never been reviewed by HEW.

III. Criteria By Which Drugs Are Scheduled

The Controlled Substances Act sets forth the findings which must be made to put a substance in any of the five schedules. These are as follows (Section 202(b)):

Schedule I

(A) The drug or other substance has a high potential for abuse.

(B) The drug or other sustance has no currently accepted medical use in treatment in the United States.

(C) There is a lack of accepted safety for use of the drug or other substance under medical supervision.

Schedule II

(A) The drug or other substance has a high potential for abuse.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.

(C) Abuse of the drug or other substances may lead to severe psychological or physical dependence.

Schedule III

(A) The drug or other substance has a potential for abuse less than the drugs or other substances in Schedules I and II.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.

Schedule IV

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule III.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule III.

Schedule V

(A) The drug or other substance has a low potential for abuse relative to the drugs or other substances in Schedule IV.

(B) The drug or other substance has a currently accepted medical use in treatment in the United States.

(C) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the

drugs or other substances in Schedule IV.

In making these findings, DEA and HEW are directed to consider eight specific factors (Section 201(c)):

(1) Its actual or relative potential for abuse;

(2) Scientific evidence of its pharmacological effect, if known;

(3) The state of current scientific knowledge regarding the drug or other substance;

(4) Its history and current pattern of abuse;

(5) The scope, duration, and significance of abuse;

(6) What, if any, risk there is to the public health;

(7) Its psychic or physiological dependence liability;

(8) Whether the substance is an immediate precursor of a substance already controlled under this title.

Perhaps the best single discussion of what these factors mean is found in the Report of the Committee on Interstate and Foreign Commerce of the House of Representatives regarding the 1970 Act (House Report 91-1444, Part 1, pp. 34-36), which reads as follows:

> A key criterion for controlling a substance, and the one which will be used most often, is the substance's potential for abuse. If the Attorney General determines that the data gathered and the evaluations and recommendations of the Secretary constitute substantial evidence of potential for abuse, he may initiate control proceedings under this section. Final control by the Attorney General will also be based on his findings as to the substance's potential for abuse.
>
> The term "potential for abuse" is found in the definition of a "depressant or stimulant drug" contained in Section 201(v) of the Federal Food, Drug, and Cosmetic Act and is characterized further in the regulations (21 CFR 166.2(e)) promulgated under that section as follows:
>
> > The Director may determine that a substance has a potential for abuse because of its depressant or stimulant effect on the central nervous system or its hallucinogenic effect if:
> >
> > (1) There is evidence that individuals are taking the drug or drugs containing such a substance in amounts sufficient to create a hazard to their health or to the safety of other individuals or of the community; or
> >
> > (2) There is significant diversion of the drug or drugs containing such a substance from legitimate drug channels; or
> >
> > (3) Individuals are taking the drug or drugs containing such a substance on their own initiative rather than on the basis of medical advice from a practitioner licensed by law to administer such drugs in the course of his professional practice; or
> >
> > (4) The drug or drugs containing such a substance are new drugs so related in their action to a drug or drugs already listed as having a potential for abuse to make it likely that the drug will have the same potentiality for abuse as such drugs, thus making it reasonable to assume that there may be significant diversions from legitimate channels, significant use contrary to or without medical advice, or that it has a substantial capability of creating hazards to the health of the user or to the safety of the community.
>
> These regulations follow and extend the suggestions contained in the report of this committee accompanying H.R. 2, 89th Congress, which became the Drug Abuse Control Amendments of 1965 (House Report No. 130, 89th Congress, first session, page 7 (1965)).
>
> The report went further in its discussion of the "potential" aspect of the term. It stated that it did not intend that potential for abuse be determined on the basis of "isolated or occasional nontherapeutic purposes." The committee felt that there must exist "a substantial potential for the occurrence of significant diversions from legitimate channels, significant use by individuals contrary to professional advice, or substantial capability of creating hazards to the health of the user or the safety of the community" (at page 7).
>
> With respect to the question of the extent to which actual, as distinguished from potential, abuse was required to be established, that report stated that "the Secretary of Health, Education, and Welfare should not be required to wait until a number of lives have been destroyed or substantial problems have already arisen before designating a drug as subject to controls of the bill" (at page 7).
>
> In speaking of "substantial" potential the term "substantial" means more than a mere

scintilla of isolated abuse, but less than a preponderance. Therefore, documentation that, say, several hundred thousand dosage units of a drug have been diverted would be "substantial" evidence of abuse despite the fact that tens of millions of dosage units of that drug are legitimately used in the same time period. The normal way in which such diversion is shown is by accountability audits of the legitimate sources of distribution, such as manufacturers, wholesalers, pharmacies, and doctors.

Misuse of a drug in suicides and attempted suicides as well as injuries resulting from unsupervised use are regarded as indicative of a drug's potential for abuse.

Aside from the criterion of actual or relative potential for abuse, subsection (c) of Section 201 lists seven other criteria, already referred to above, which must be considered in determining whether a substance meets the specific requirements specified in Section 202(b) for inclusion in particular schedules and accordingly should be designated a controlled substance under a given schedule (including transfer from any other schedule) or removed entirely from the schedules. A brief discussion of each of these criteria follows.

(1) *Scientific evidence of its pharmacological effects.*—The state of knowledge with respect to the effects of uses of a specific drug is, of course, a major consideration, e.g., it is vital to know whether or not a drug has an hallucinogenic effect if it is to be controlled because of that. The best available knowledge of the pharmacological properties of a drug should be considered.

(2) *The state of current scientific knowledge regarding the substance.*—Criteria (1) and (2) are closely related. However, (1) is primarily concerned with pharmacological effects and (2) deals with all scientific knowledge with respect to the substance.

(3) *Its history and current pattern of abuse.*—To determine whether or not a drug should be controlled, it is important to know the pattern of abuse of that substance, including the social, economic, and ecological characteristics of the segments of the population involved in such abuse.

(4) *The scope, duration, and significance of abuse.*—In evaluating existing abuse, not only must the Attorney General know the pattern of abuse, but he must know whether the abuse is widespread. He must also know whether it is a passing fad, or whether it is a significant chronic abuse problem like heroin addiction. In reaching his decision, the Attorney General should consider the economics of regulation and enforcement attendant to such a decision. In addition, he should be aware of the social significance and impact of such a decision upon those people, especially the young, that would be affected by it.

(5) *What, if any, risk there is to the public health.*—If a drug creates no danger to the public health, it would be inappropriate to control the drug under this bill.

(6) *Its psychic or physiological dependence liability.*—There must be an assessment of the extent to which a drug is physically addictive or psychologically habit forming, if such information is known.

(7) *Whether the substance is an immediate precursor of a substance already controlled.*—The bill allows inclusion of immediate precursors on this basis alone into the appropriate schedule and thus safeguards against possibilities of clandestine manufacture.

It should be noted that the above-mentioned factors do not require specific findings to be made with respect to control under, or removal from, schedules, but rather are factors to be considered in making the special findings required under Section 202(b) for control under such schedules.

While these criteria and factors seem very clear in the abstract, there are underlying difficulties. Drugs with no currently accepted medical use in the United States, if they are to be controlled at all, must be placed in Schedule I. Thus all research drugs, as well as drugs as disparate as heroin, LSD, and marihuana, are in Schedule I. There is some concern that this may inhibit basic research in these substances. Secondly, among Schedules II, III, IV and V, Congress has not provided significant guidance in determining what weight should be given to individual factors of abuse. The statute considers physical dependence as a more serious concern than psychological dependence; for placement in Schedule III, for example, a drug may have a moderate or low degree of physical dependence but must

have a high degree of psychological dependence. The statute and legislative history are silent, however, on such questions as: Is organic harm more serious than psychological harm? Is long-term physical deterioration more serious than acute toxicity? What weight should be given to mutagenic and teratogenic effects? Is task-related misuse (e.g., truck drivers using stimulants) less serious than recreational use (e.g., teenagers using drugs on weekends)? Is white-collar drug abuse (e.g., housewives taking stimulants and depressants for non-indicated uses) more serious than abuse by minority groups (e.g., youths or blacks)?

Ultimately, the committee will be facing these kinds of questions; for these issues are at the heart of determining the relative potential for abuse and relative actual abuse of various drugs and of determining which level of control should be imposed on specific drugs.

The Report of the House Committee suggests the kind of evidence needed to establish a case to control a drug. It should be emphasized that this evidence varies depending on the type of situation involved. For example, several drugs have recently been controlled which have never been marketed in the United States or in the world. Data on actual abuse of these drugs, including patterns, duration, and scope, are nonexistent. These drugs, however, are similar in chemical structure or pharmacological activity to drugs of known potential for abuse. In a case to establish the abuse potential of these drugs, the evidence therefore revolved around the degree of similarity or dissimilarity between the drugs in question and controlled drugs with a known abuse potential. Another example is found in the recent hearing to place methaqualone in Schedule II. The only issue in dispute was whether methaqualone produced a physical dependence. The Government contended that it did, and one of the manufacturers argued that there was no evidence to support this claim. When the hearing commenced, there was no conclusive literature on this point. Several physicians dealing in drug abuse, however, had sufficient experience to conclude in their own minds that physical dependence liability did in fact result from methaqualone abuse. As a result their expert testimony was used in establishing the Government's case in the absence of any well-controlled scientific experiment which demonstrated a dependence-creating liability for methaqualone. These and other experiences indicate the difficulty in giving any hard-and-fast rules on the types of evidence needed to place a drug in a schedule.

The Controlled Substances Act also prescribes the quantity of evidence needed to place a drug in a schedule. Section 507 states that "findings of fact . . ., if supported by substantial evidence, shall be conclusive." In 1966, the Supreme Court made the following observations on the meaning and purpose of the "substantial evidence" test (*Consolo* v. *Federal Maritime Commission,* 383 U.S. 607, 619-621; 86 S. Ct. 1018, 1026-27; citations and footnotes omitted):

> We have defined "substantial evidence" as "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." . . . This is something less than the weight of the evidence, and the possibility of drawing two inconsistent conclusions from the evidence does not prevent an administrative agency's finding from being supported by substantial evidence.
>
> Congress was very deliberate in adopting this standard of review. It frees the reviewing courts of the time-consuming and difficult task of weighing the evidence, it gives proper respect to the expertise of the administrative tribunal, and it helps promote the uniform application of the statute. These policies are particularly important when a court is asked to review an agency's fashioning of discretionary relief. In this area agency determinations frequently rest upon a complex and hard-to-review mix of considerations. By giving the agency discretionary power to fashion remedies, Congress places a premium upon agency expertise, and, for the sake of uniformity, it is usually better to minimize the opportunity for reviewing courts to substitute their discretion for that of the agency.

Courts and legal scholars have struggled for at least forty years to produce a clear, simple statement of the "substantial evidence" test. For present purposes, the following may suffice:

A conclusion regarding any aspect of a drug—pharmacology, abuse, dependence liability—will be upheld if the record contains relevant and reliable evidence from which a reasonable man, acting reasonably, could draw the same conclusion. The conclusion will be upheld even though the record also contains relevant and reliable evidence from which a reasonable man, acting reasonably, could draw an opposite conclusion. Thus, the conclusion need not be established "beyond a reasonable doubt" or even "by a preponderance of the evidence."

Glossary of Slang Terms for Drugs

Amphetamines	Beans, Bennies, Black Beauties, Blackbirds, Black Mollies, Bumblebees, Cartwheels, Chalk, Chicken Powder, Copilots, Crank, Crossroads, Crystal, Dexies, Double Cross, Eye Openers, Hearts, Jelly Beans, Lightning, Meth, Minibennies, Nuggets, Oranges, Pep Pills, Speed, Roses, Thrusters, Truck Drivers, Turnabouts, Uppers, Ups, Wake-ups
Barbiturates	Barbs, Block Busters, Bluebirds, Blue Devils, Blues, Christmas Trees, Downers, Green Dragons, Marshmallow Reds, Mexican Reds, Nebbies, Nimbies, Peanuts, Pink Ladies, Pinks, Rainbows, Red and Blues, Redbirds, Red Devils, Reds, Sleeping Pills, Stumblers, Yellow Jackets, Yellows.
Cocaine	Bernice, Bernies, Big C, Blow, C, Coke, Dream, Flake, Girl, Gold Dust, Heaven Dust, Nose Candy, Paradise, Rock, Snow, White
Glutethimide	C.D., Cibas
Hashish	Black Russian, Hash, Kif, Quarter Moon, Soles
Heroin	Big H, Boy, Brown, Brown Sugar, Caballo, Chinese Red, Chiva, Crap, Doojee, H, Harry, Horse, Junk, Mexican Mud, Powder, Scag, Smack, Stuff, Thing
LSD	Acid, Beast, Big D, Blue Cheer, Blue Heaven, Blue Mist, Brown Dots, California Sunshine, Chocolate Chips, Coffee, Contact Lens, Cupcakes, Haze, Mellow Yellows, Microdots, Orange Mushrooms, Orange Wedges, Owsley, Paper Acid, Royal Blue, Strawberry Fields, Sugar, Sunshine, The Hawk, Wedges, White Lightning, Window Pane, Yellows
Marihuana	Acapulco Gold, Broccoli, Bush, Dry High, Gage, Ganga, Grass, Griffo, Hay, Hemp, Herb, J, Jay, Jane, Mary Jane, Mota, Mutah, Panama Red, Pod, Pot, Reefer, Sativa, Smoke, Stick, Tea, Weed
MDA	Love Drug
Mescaline	Beans, Buttons, Cactus, Mesc, Mescal, Mescal Buttons, Moon
Methamphetamines	Crystal, Meth, Speed
Methaqualone	Quas, Quads, Soapers, Sopes
Morphine	Cube, First Line, Hocus, Miss Emma, Morf, Morpho, Morphy, Mud
Phencyclidine	Angel Dust, DOA (Dead On Arrival), Hog, Killer Weed (when combined with marihuana or other plant material), PCP, Peace Pill
Psilocybin/Psilocyn	Magic Mushroom, Mushroom

Bibliography

Chemical Compositions

American Drug Index, Philadelphia, J. B. Lippincott Co., 1975

Claus, E. P., Tyler, V. E., and Brady, L. R., *Pharmacognosy*, 6th ed., Philadelphia, Lea and Febiger, 1970

The Merck Index, 8th ed., Rahway, N.J., Merck and Co., Inc., 1968

Schultes, R. E. and Hofmann, A., *The Botany and Chemistry of Hallucinogens*, Springfield, Ill., Charles C. Thomas, 1973

Usdin, E. and Efron, D. H., *Psychotropic Drugs and Related Compounds*, Washington, D.C., U.S. Government Printing Office, 1972

Uses and Effects

Bourne, P. G., editor, *A Treatment Manual for Acute Drug Abuse Emergencies*, Rockville, Md., National Clearinghouse for Drug Abuse Information, 1974

Goodman, L. S. and Gilman, A., editors, *The Pharmacological Basis of Therapeutics*, 4th ed., New York, Macmillan, 1970

Isbell, H. and Chrusciel, T. L., *Dependence Liability of "Non-Narcotic" Drugs*, Geneva, World Health Organization, 1970

Kalant, Oriana J., *The Amphetamines: Toxicity and Addiction*, 2nd ed., Springfield, Ill., Charles C. Thomas, 1973

Marihuana and Health, Fourth Report to the U.S. Congress from the Secretary of Health, Education, and Welfare, No. (ADM) 75-181, Washington, D.C., U.S. Government Printing Office, 1974

Martindale—The Extra Pharmacopoeia, 26th ed., London, The Pharmaceutical Press, 1972

Physicians' Desk Reference, Oradell, N.J., Medical Economics Co., 1975

Remington's Pharmaceutical Sciences, 14th ed., Easton, Pa., Mack Publishing Co., 1970

United Nations, Department of Social Affairs, "Heroin," *Bulletin on Narcotics*, Vol. V, No. 2, pp. 3-73, April-June, 1953

Wilson, C. O., Gisvold, O., and Doerge, R. F., editors, *Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 6th ed., Philadelphia, Pa., J. B. Lippincott Co., 1971

Other Recommended Reading

Blum, R. H., *Society and Drugs*, San Francisco, Jossey-Bass, 1969

Blum, R. H., *Students and Drugs*, San Francisco, Jossey-Bass, 1969

Brecher, Edward M., et al, *Licit and Illicit Drugs: The Consumer's Union Report*, Boston, Little Brown and Co., 1972

Chein, I., Gerard, D. L., Lee, R. S., and Rosenfeld, E., *The Road to H: Narcotics, Delinquency and Social Policy*, New York, Basic Books, 1964

Fort, J., *Pleasure Seekers. The Drug Crisis, Youth and Society*, Indianapolis, Bobbs-Merrill, 1969

Goode, Erich, *Drugs in American Society*, New York, Alfred A. Knopf, 1972

Horman, Richard E. and Fox, Allan M., editors, *Drug Awareness: Key Documents on LSD, Marihuana, and the Drug Culture*, New York, Avon, 1969

National Clearinghouse for Drug Abuse Information, *Resource Book for Drug Abuse Education*, 2nd ed., Washington, D.C., U.S. Government Printing Office, 1972

Nowlis, H. G., *Drugs on the College Campus*, Garden City, N.Y., Doubleday, 1968

Smith, D. E. and Wesson, D. R., editors, *Uppers and Downers*, Englewood Cliffs, N.J., Prentice-Hall, Inc., 1973

Stewart, W. Wayne, editor, *Drug Abuse in Industry*, Miami, Halos, 1970

Zarafonetis, C. J. D., editor, *Drug Abuse: Proceedings of the International Conference*, Ann Arbor, 1970, Philadelphia, Lea and Febiger, 1972

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