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ORIGINAL ARTICLE

Long-term benefits of single-dose psilocybin in depressed patients with cancer

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Abstract

Background: Patients with cancer often struggle with depression, which can negatively impact quality of life as well as be challenging to manage.

Methods: A phase 2 trial was conducted that demonstrated safety, feasibility, and efficacy of a single dose of psilocybin combined with psychological support in a community cancer setting in 30 patients with cancer and a major depressive disorder. Here, efficacy outcomes at 2 years' follow-up are reported.

Results: Of 28 patients, 15 (53.6%) demonstrated significant reduction in depression as measured by the Montgomery Asberg Depression Rating Scale (average, −15.0 points from baseline; $p < .001$), and 14 (50%) had sustained depression reduction. Thirteen patients (46.4%) experienced significant reduction in anxiety as measured by the Hamilton Anxiety Rating Scale (average, −13.9 points from baseline, $p < .001$), and 12 (42.9%) had sustained anxiety reduction.

Conclusions: These findings demonstrate robust antidepressive activity from a single 25 mg dose of psilocybin combined with psychotherapy and suggest a potentially paradigm-changing alternative to traditional antidepressants requiring further study.

KEYWORDS

antidepressant, cancer, depression, psilocybin, psychotherapy

Approximately 25% of people living with cancer have depression that can impact treatment outcomes.[1–3] Physicians have limited tools to effectively manage mental health care in these patients. Psilocybin has demonstrated efficacy in treating depression; however, there are no data on its long-term effectiveness for depression.

We evaluated the length of impact of psilocybin combined with psychological support in 30 patients with cancer and diagnosed with major depression disorder (MDD). By 2 months, 80% of patients experienced significant reduction in depression severity scores.[4,5] This report evaluates depression reduction at 24 months.

METHODS

Design, eligibility, treatment, endpoints, and statistical analyses of this phase 2, single-center, fixed-dose, open-label study have been previously described.[4,5] Briefly, 30 adults with curable or noncurable cancer and major depression disorder not taking an antidepressant and/or antipsychotic medications or medical cannabis at screening and without suicide risk were enrolled. The study was approved by the Advarra institutional review board, and patients provided written consent before participation.

Participants were grouped into cohorts of three to four for group and individual (1:1 therapist-to-patient ratio) preparatory psycho

therapy. Following a screening period that included two visits (initial screening and an individual preparatory session with the assigned therapist), patients participated in two baseline preparation sessions (one group and one individual). Each patient then received one 25-mg dose of psilocybin in a single 6- to 7-hour session. Following psilocybin treatment, patients participated in two group and two individual integration sessions, and follow-up took place. Each cohort completed screening, baseline assessment, treatment, 8 hours of preparation and integration therapy, and follow-up. The entire process included a total of eight visits over the course of 8 weeks.

Mental health improvement was measured at 2, 18, and 24 months with the Montgomery Asberg Depression Rating Scale (MADRS) and Hamilton Anxiety Rating Scale (HAM-A). Significant depression reduction was calculated as participants who had ≥50% reduction in MADRS/HAM-A score. Sustained reduction was calculated as participants who had ≥0% reduction in MADRS/HAM-A score at both visits, week 8, and 24 months' follow-up. Remission was calculated as MADRS score ≤10 or HAM-A score ≤7 at 24 months' follow-up.

RESULTS

Two patients died, leaving 28 of 30 patients for the 24-month analysis of effectiveness. The median age at enrollment was 57.5 years; the majority were female and White (Table 1).

Over 24 months, no patients were hospitalized for depression, 60.7% (17/28) did not receive additional psychiatric medications, and 60.7% (17/28) did not use additional psychedelics (Table 1). Alcohol use decreased in 21.4% (6/28) of patients after psilocybin treatment.

Of the 28 patients, 89.3% (25) experienced significant depression reduction at 2 months in the MADRS (average of −20.0 points from baseline, $p < .001$). At 24 months' follow-up, 53.6% (15) had significant reduction in the MADRS (average of −15.0 points from baseline; $p < .001$; Figure 1A). At 24 months, 50% (14) had sustained depression reduction as well as remission.

Twenty-five percent (seven) experienced sustained reduction in depression at 24 months from a single psilocybin dose without any additional psychedelic or antidepressant treatments. Among the others, 25% (seven) received antidepressants after psilocybin and three of those received a second psychedelic treatment.

At 2 months, 78.6% (22) experienced significant reduction in anxiety in the HAM-A (average of −17.0 points from baseline, $p < .001$), with 46.4% (13) having significant reduction at 24 months (average of −13.9 points from baseline, $p < .001$; Figure 1B). Overall, 17.9% (five) experienced significant reduction in anxiety at 24 months from a single dose of psilocybin without any additional psychedelic or antidepressant treatments. Additionally, 12 patients (42.9%) experienced sustained anxiety reduction at 24 months'

TABLE 1 Baseline demographics and medical history since treatment with psylocybin.

	Total $N = 28$
Age at initial treatment, median (range)	57.5 years (30–78)
Sex, *n* (%)	
Female	19 (67.9)
Male	9 (32.1)
Ethnicity, *n* (%)	
African American/Black	3 (10.7)
Asian, Asian American, Pacific Islander	2 (7.1)
Caucasian	22 (78.6)
Hispanic, Latin	1 (3.6)
Hospitalization for depression, *n* (%)	
Yes	0
No	22 (78.6)
Missing	6 (21.4)
Number of psychiatric medications, *n* (%)	
0	17 (60.7)
1	3 (10.7)
2	1 (3.6)
3	1 (3.6)
Missing	6 (21.4)
Group or individual psychotherapy, *n* (%)	
Yes	18 (64.3)
No	4 (14.3)
Missing	6 (21.4)
Use of psychedelic drugs, *n* (%)	
Yes	5 (17.9)
No	17 (60.7)
Missing	6 (21.4)
Changes in alcohol consumption patterns, *n* (%)	
Yes, increased	0
Yes, decreased	6 (21.4)
No	16 (57.1)
Missing	6 (21.4)
New substances or change in frequency of substance use, *n* (%)	
Yes, increased	2 (7.1)
Yes, decreased	1 (3.6)
No	19 (67.9)
Missing	6 (21.4)

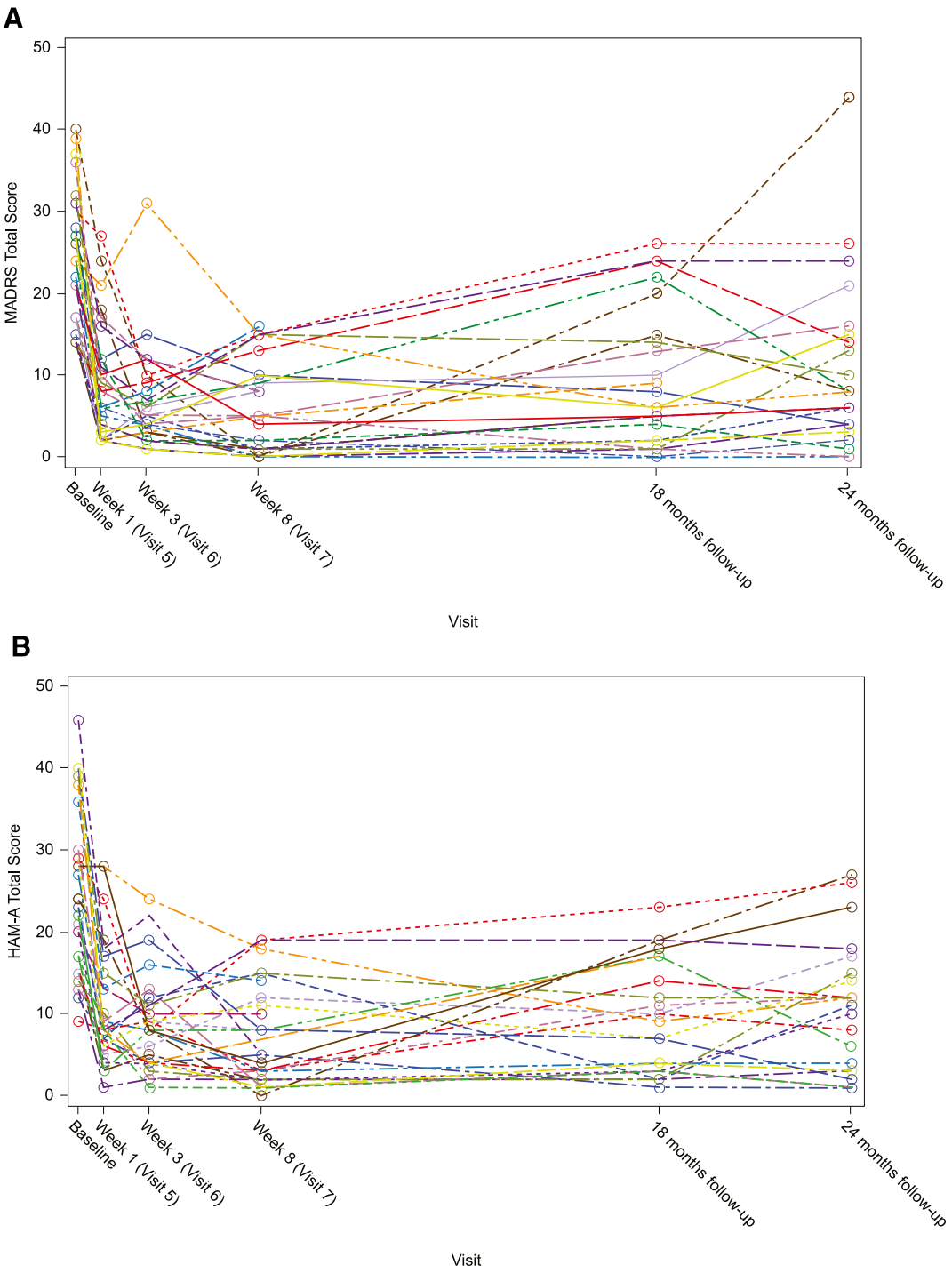

FIGURE 1 Individual MADRS scores (A) and HAM-A scores (B) at baseline, week 1, week 3, week 8, 18 months, and 24 months following psilocybin treatment. HAM-A indicates Hamilton Anxiety Rating Scale; MADRS, Montgomery Asberg Depression Rating Scale.

follow-up, of which 58.3% (7) received antidepressants after psilocybin; two of those also received another psychedelic treatment.

DISCUSSION

For 50% of depressed patients with cancer, a single 25-mg dose of psilocybin combined with psychotherapy showed continued remission from depression at 24 months. Moreover, for 25% of patients, the sustained reduction in depression did not require additional psychedelic or antidepressant medications. Similarly, psilocybin reduced anxiety for 43% of patients at 24 months.

Findings from a meta-analysis evaluating antidepressants, including selective serotonin reuptake inhibitors, for the treatment of depression in cancer patients showed only a small potential benefit at 6 to 12 weeks (standard mean difference −0.52; 95% CI, −0.92 to 0.12), with very low certainty of the evidence and no follow-up beyond 12 weeks.[6] Our findings suggest psilocybin may be an

alternative to traditional antidepressants in providing long-term mental health treatment for patients with cancer.

As the body of evidence demonstrating the safety and benefits of psilocybin in reducing anxiety and depression in patients with cancer continues to grow, additional clinical research is needed given its potential to address an unmet need. Important questions around which types of therapy work best with psilocybin, whether additional doses of treatment help those who did not achieve remission, and whether selective serotonin reuptake inhibitors can be concomitantly administered with psilocybin will need to be investigated in future studies. Indeed, an ongoing randomized, double-blind, trial evaluating a single 25-mg dose of psilocybin or placebo as treatment for anxiety, depression, and existential distress in patients with advanced cancer, will help provide much needed evidence to move psilocybin toward a mainstay pharmacologic intervention to help our patients with cancer struggling with depression.[7]

Psilocybin and psychotherapy can provide up to 24 months of sustained relief for depression and anxiety for a substantial portion of depressed cancer patients. These results offer promise for a novel and long-lasting therapeutic approach to address mental health challenges cancer patients face, underscoring the urgent need for continued evaluation clinical trials.

AUTHOR CONTRIBUTIONS

Manish Agrawal: Conceptualization; methodology; data curation; formal analysis; writing—original draft; writing—review & editing; funding acquisition; project administration; supervision. **Kim Roddy**: Conceptualization; data curation; writing—review & editing; funding acquisition; supervision; project administration; writing—original draft; methodology. **Betsy Jenkins**: Conceptualization; data curation; writing—review & editing; project administration; supervision; methodology. **Celia Leeks**: Data curation; project administration; supervision. **Ezekiel Emanuel**: Conceptualization; methodology; data curation; formal analysis; supervision; project administration; writing—original draft; writing—review & editing.

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CONFLICT OF INTEREST STATEMENT

Ezekiel Emanuel reports personal fees from UnitedHealth Group, Blue Cross Blue Shield, CBI/Informa, RISE Health, Galien Foundation, Rightway, Signature Healthcare Foundation, Healthcare Leaders of New York, MedImpact, Princeton University, Philadelphia Committee on Foreign Relations, Yale University, Hartford Medical Society, Global Innovation Forum, the Hawaii Medical Service Association and Queen's Health System, Macalester College, Advocate Aurora Health Summit, DPharm, University of Pittsburgh Shadyside Medical Center, University of California, San Francisco Department of Urology, Advocate Aurora Health, Cain Brothers, and Bowdoin College; serving as an uncompensated speaker, panelist, or moderator for Center for Global Development, American Academy of Arts and Sciences, University of California, San Francisco, World Affairs, Unite Us, University of Pennsylvania Engaging Minds, Vagelos College of Physicians and Surgeons, United Nations Educational, Scientific and Cultural Organization Global Conference, School of Pharmaceutical and Biotech Business, National Institutes of Health Demystifying Medicine Series, American Society of Preventive Oncology 45th Annual Meeting, Blue Cross Blue Shield National Customer Advisory Council, University of Pennsylvania Cellicon Valley 2021, Independent Health and Aged Care Pricing Authority Activity Based Funding Conference, University of Pennsylvania Leonard Davis Institute of Health Economics, Penn Medicine Alumni Weekend, National Health Equity Summit, Galien Foundation, Temple Sholom of Chicago, Perry World House Graduate Association, the Italian Medicine Agency, Penn Rising Scholar Success Academy, Syllable and Oak Portico, Rainbow PUSH Coalition, Infectious Diseases Society of America, VinFuture, Leonard David Institute, Brown University, Organisation for Economic Co-operation and Development, 21st Population Health Colloquium, VillageMD, University of Pennsylvania College of Liberal and Professional Studies, University of Sydney, Tel Aviv University, American Philosophical Society, Health Action Alliance, Yale University, Association of Bioethics Program Directors Spring Meeting, Icahn School of Medicine at Mount Sinai, Abramson Cancer Center, University of Minnesota, Institute for Peace and Security Studies Addis Conference, Faith Health Alliance, The Wharton School at the University of Pennsylvania, Oak CEO Summit, Centers for Disease Control and Prevention, American Academy of Political and Social Science, Primary Care Transformation, 16th World Congress of Bioethics, Blue Cross Blue Shield Alliance for Health Research, White House Cancer Moonshot, BC Philadelphia, American Society of Clinical Oncology Quality Care Symposium, and Brookings Institution; serving on the board of advisors of Notable, external advisory board of VillageMD, advisory board of Health Innovation Exchange, internal advisory board of Colton Center for Autoimmunity, advisory board of JSL Health Fund, expert advisory board of the World Health Organization COVID-19 Ethics & Governance Working Group, and advisory board of President Biden's Transition COVID-19 Committee; and serving as special advisor to the World Health Organization director general, member of the advisory board of the Peterson Foundation, advisor for Clarify Health, unpaid board member for Oncology Analytics, founding member of COVID-19 Recovery LLC, founding partner of Embedded LLC, venture partner of Oak HC/FT, and a member of the board of advisors for Cellares. Manish Agrawal, Kim Roddy, Betsy Jenkins, and Celia Leeks are employed by Sunstone Therapies. No other disclosures were reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

INFORMED CONSENT/PATIENT CONSENT

This study was approved by the Advarra institutional review board, sponsored by Maryland Oncology Hematology, PA. Written consent was obtained from each participant before participation.

TRIAL REGISTRATION NUMBER/DATE

NCT04593563; September 1, 2020.

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