Original Article

Long-term follow-up of psilocybin-assisted psychotherapy for psychiatric and existential distress in patients with life-threatening cancer

Journal of Psychopharmacology
1–12

DOI: 10.1177/0269881119897615
journals.sagepub.com/home/jop
SAGE

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Abstract

Background: A recently published randomized controlled trial compared single-dose psilocybin with single-dose niacin in conjunction with psychotherapy in participants with cancer-related psychiatric distress. Results suggested that psilocybin-assisted psychotherapy facilitated improvements in psychiatric and existential distress, quality of life, and spiritual well-being up to seven weeks prior to the crossover. At the 6.5-month follow-up, after the crossover, 60–80% of participants continued to meet criteria for clinically significant antidepressant or anxiolytic responses.

Methods: The present study is a long-term within-subjects follow-up analysis of self-reported symptomatology involving a subset of participants that completed the parent trial. All 16 participants who were still alive were contacted, and 15 participants agreed to participate at an average of 3.2 and 4.5 years following psilocybin administration.

Results: Reductions in anxiety, depression, hopelessness, demoralization, and death anxiety were sustained at the first and second follow-ups. Within-group effect sizes were large. At the second (4.5 year) follow-up approximately 60–80% of participants met criteria for clinically significant antidepressant or anxiolytic responses. Participants overwhelmingly (71–100%) attributed positive life changes to the psilocybin-assisted therapy experience and rated it among the most personally meaningful and spiritually significant experiences of their lives.

Conclusion: These findings suggest that psilocybin-assisted psychotherapy holds promise in promoting long-term relief from cancer-related psychiatric distress. Limited conclusions, however, can be drawn regarding the efficacy of this therapy due to the crossover design of the parent study. Nonetheless, the present study adds to the emerging literature base suggesting that psilocybin-facilitated therapy may enhance the psychological, emotional, and spiritual well-being of patients with life-threatening cancer.

Keywords
Psilocybin, psychedelic, cancer, depression, anxiety

Introduction

Cancer is a leading cause of morbidity and mortality globally, with approximately 14 m new diagnoses made annually (Ferlay et al., 2013). Despite technological advancements that have led to earlier detection and significantly improved medical treatments for cancer, the diagnosis still provokes intense fear and distress among many patients (Lee, 2008). It is common for cancer patients to develop psychiatric distress with rates of anxiety and depressive disorders as high as 40% in hospital settings (Mitchell et al., 2011). Medical providers often neglect or inadequately address these symptoms (Gouveia et al., 2015). Clinically significant depression and anxiety among cancer patients are associated with several poor outcomes including decreased quality of life and cancer survival rates, reduced treatment adherence, and increased desire for death and rates of suicide (Amiri and Behnezhad, 2019; Jaiswal et al., 2014).

Psycho-oncology is increasingly recognizing the unique existential challenges accompanying a cancer diagnosis (Breitbart et al., 2000). Existential distress has been described as mental distress experienced by those facing imminent death and associated with demoralization, absence of purpose or meaning, hopelessness, isolation, and loss of dignity (Kissane, 2000; Murata, 2003). Psychotropic medications are commonly used to treat cancer-related distress, but evidence supporting efficacy is limited and inconsistent (Grassi et al., 2014; National Comprehensive Cancer Network, 2014), and significant side effects have been found to adversely affect treatment compliance

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(Li et al., 2012). Several meta-analyses of placebo-controlled trials of antidepressants have failed to demonstrate a clear effect of treatment over placebo in cancer patients (Iovieno et al., 2011; Laoutidis and Mathiak, 2013; Ostuzzi et al., 2015). Psychosocial interventions have been developed to specifically target the existential and spiritual distress of cancer patients, albeit with limited efficacy (Chochinov et al., 2011; LeMay and Wilson, 2008) and relatively weak methodological study designs (Xing et al., 2018). There is a compelling need to develop more rigorous, well-designed trials that adequately assess the efficacy of existing spiritual and existential interventions. There is also a need to develop novel interventions that can increase the effect sizes of interventions aimed at improving the psychospiritual states of people with cancer.

In response to the limited evidence supporting the efficacy of existing approaches to treating psychiatric and existential distress, researchers have deployed attention toward examining the therapeutic potential of serotonergic psychedelics (Reiche et al., 2018). Historically, classic psychedelics were studied as novel therapeutic agents in the psychiatric treatment of patients with cancer. In the 1950s and 1960s researchers funded by the National Institute of Mental Health (NIMH) conducted trials with hundreds of participants and found that psychedelics such as d-lysergic acid diethylamide (LSD) alleviated depression, anxiety, and pain, and improved sleep and quality of life associated with cancer (Kast, 1970; Kast and Collins, 1964; Grof et al., 1973). After a quiescence of over two decades, clinical trials with the classical psychedelics resumed. Four recently published crossover randomized controlled trials (RCTs) administered psilocybin (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016) and LSD (Gasser et al., 2014; 2015) with psychological support to participants with cancer diagnoses or life-threatening illnesses (N=104) and established overall safety and preliminary efficacy with medium to large effects. Despite the promising evidence regarding the acute therapeutic effects of psychedelics, there is a modest amount of data suggesting safety and efficacy of these interventions in the long-term. The longest follow-up in these studies occured at 12 months post-crossover in one of these trials, at which time significant reductions in anxiety were sustained following two doses of LSD combined with psychotherapy (Gasser et al., 2015).

The present study is a long-term follow-up (LTFU) analysis of a randomized placebo-controlled trial that compared a single dose of psilocybin (0.3 mg/kg) with a single dose of niacin (250 mg) in conjunction with psychotherapy in patients (N=29) with cancer-related psychiatric and existential distress (Ross et al., 2016). In the parent trial, results suggested that psilocybin-assisted psychotherapy catalyzed rapid antidepressant and anxiolytic effects with large effect sizes and rates of clinical response up to seven weeks (prior to study crossover). After the crossover at the final (6.5-month) point, approximately 60–80% of patients met the criteria for clinically significant antidepressant or anxiolytic responses. Psilocybin also appeared to yield acute and sustained reductions in demoralization and hopelessness, as well as improvements in spiritual well-being and quality of life. There were no significant improvements in death anxiety. Seventy percent of participants rated the experience as the single or top-five most personally meaningful experience(s) of their lives, and 52% rated it the single or top-five most spiritually significant experience(s) of their lives. Ratings of mystical-type experiences were found to partially mediate the effect of psilocybin versus placebo on anxiety and depression outcomes (Ross et al., 2016). Limited conclusions, however, can be drawn regarding the efficacy of psilocybin-assisted therapy beyond the seven-week point due to the crossover design. The objective of the present study was to determine whether benefits reported at parent study completion were maintained at two extended LTFU points.

Methods

The NYU School of Medicine Institutional Review Board approved a protocol amendment for the addition of the LTFU data collection. Participants in this present study had previously concluded treatment in our parent study (for full details of this study see Ross et al., 2016). Of the original 29 participants, we contacted all 16 participants who were not deceased at the time of LTFU (the remaining 13 participants were deceased). All of these participants had agreed to be contacted about future research opportunities. Of the 16 participants who were contacted, 15 agreed to participate in the LTFU and completed measures through a secure online portal. One participant died (from cancer-related complications) after completing the first LTFU and prior to the second LTFU, leaving us with 14 participants at the second LTFU. The first and second LTFUs occurred on average 3.2 years (range 2.3–4.5 years) and 4.5 years (range 3.5–5.5 years) following the participants' psilocybin dosing date, respectively.

In the parent study, participants were randomly assigned to one of two groups: psilocybin (0.3 mg/kg) on the first medication session followed by niacin (250 mg) on the second session (i.e. psilocybin-first group), or niacin (250 mg) on the first medication session followed by psilocybin (0.3 mg/kg) on the second session (i.e. niacin-first group). Participants received nine total preparatory psychotherapy sessions and post-medication integration sessions delivered by a dyadic therapy team. The trial employed a crossover design at seven weeks following the first drug administration, with the final outcome assessment at 6.5 months following the second drug administration (i.e. after the crossover).

Participants

Demographic information is presented in Table 1. At the first LTFU, the mean age of participants was 53 years old (standard deviation (SD)=16 years), and they were predominantly female (60%). The majority was non-Hispanic White (93%), followed by Asian (6%). Forty percent reported Catholic/Christian or Jewish beliefs, and one-third (33%) reported atheist/agnostic beliefs, followed by "other" faith/tradition (13%). Gynecological cancers (33%) comprised the majority of disease sites, followed by breast (20%) and lymphomas (20%). Slightly more than half (60%) were diagnosed with early stage (I–II) cancers versus later stage (III–IV; 53%) at the parent study end point. Of note, at the second LTFU, 71% of participants had reportedly entered partial or complete remission from their cancers, and 29% were in the active stages of their diseases. Approximately half (53%) of all participants reported one or more occasions of prior hallucinogen use. The majority of participants (93%) met Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000) criteria for cancer-related adjustment disorder with anxious and/or depressed features, followed by generalized anxiety disorder (7%). Compared to the parent study sample (Ross et al., 2016), the proportions of current study participants were roughly

Table 1. Demographic and clinical characteristics of study participants at LTFU follow-ups.

Characteristic	Categories	Total	
		N=15	
Sex	Female	9	60.00%
	Male	6	40.00%
Age at follow-up; mean (SD)	Range 25–73	53 (15.5)	
Race	White/Caucasian	14	93.33%
	Asian	1	6.67%
Religious/ spiritual beliefs	Atheist/agnostic	5	33.33%
	Jewish	3	20.00%
	Catholic	1	6.67%
	Other Christian	2	13.33%
	Other faith/tradition	2	13.33%
Site of cancer	Breast	3	20.00%
	Reproductive	5	33.32%
	Lymphoma/leukemia	3	20.00%
	Other types	4	26.67%
Stage of cancer	Stage IV	2	13.33%
	Stage III	4	26.67%
	Stage II	3	20.00%
	Stage I	5	33.32%
	Other	1	6.67%
SCID (DSM-IV-TR) diagnosis	Adjustment disorder w/ anxiety and depressed mood, chronic	2	13.33%
	Adjustment disorder w/ anxiety, chronic	12	80.00%
	Generalized anxiety disorder	1	6.67%
Hallucinogen use	No	8	53.33%
	Yes	7	46.67%
Education	Part-college	2	13.33%
	Graduated 4-year college	4	26.67%
	Completed grad/professional school	9	60.00%

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders; SD: standard deviation; SCID: Structured Clinical Interview for DSM Disorders.

equivalent in all demographic variables with the exception of cancer type. There was a greater proportion of reproductive cancer in this LTFU sample than in the parent sample, and no participants carried a diagnosis of digestive cancers in the LTFU sample (compared to 21% in the parent sample).

Psychiatric interventions received during follow-up period and adverse events

A total of 13 out of the 14 participants who completed the second LTFU time point provided information regarding their use of psychotherapy or pharmacological interventions after completion of the parent study. One participant who participated in the LTFU passed away prior to the administration of this assessment. Participants provided the name, dosage, duration, and reason for medication prescription, as well as type, duration, and reason for any psychotherapy intervention received during the LTFU period. Eight participants (53%) reported taking medication daily for anxiety or depression at study screening but discontinued prior to enrollment due to the parent study exclusion criteria. Participants were allowed to take prescribed Benzodiazepines on an as needed basis up to three days prior to their first medication session. During the LTFU period five participants reported (39%) receiving some form of psychotherapy since completion of the parent trial, with one (8%) receiving psychotherapy specifically targeting cancer-related psychological distress. Three participants (23%) received some form of psychotropic drug treatment, with no participants receiving psychotropic medication specifically targeting cancer-related psychological distress during the LTFU period. None of the participants reported lasting negative or adverse effects from the psilocybin-assisted therapy experiences.

Measures

In the parent trial, primary measures were administered at the following time points: baseline, one day before and one day after the first and second drug administrations, two weeks and six weeks after the first and second drug administrations, and 26 weeks (6.5 months) after the second drug administration. Secondary measures were administered at baseline, two weeks and six weeks after the first and second drug administrations, and 26 weeks (6.5 months) after the second drug administration. The following measures were re-administered to participants at the two LTFU points in the present study.

Primary measures

Anxiety and depression measures. The Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983) is widely used in hospital settings to screen for the severity of anxiety and depression. It contains 14 questions rated on a four-point scale (total score (HAD-T) ranges from 0–56). Subscale scores can be calculated for depression (HADS-D) and anxiety (HADS-A). Although there is no single accepted cut-off score, the instrument's authors suggest that subscale scores equal to or above eight and full-scale scores over 12 indicate the possible presence of a clinical disorder (Snaith and Zigmond, 1994). The HADS has shown good reliability (Cronbach's α ranging from 0.80–0.93) and has been well validated (Herrmann, 1997).

The Beck Depression Inventory-II (BDI-II; Beck et al., 1988) is a widely used self-report screening measure for depression. The BDI-II consists of 21 questions about depressive symptoms experienced over the past two weeks rated on a three-point scale (total score ranges from 0–63). Scores above 12 indicate possible clinical depression. This measure has shown good reliability (internal consistency of 0.90) and factorial validity (Storch et al. 2004).

The State-Trait Anxiety Inventory (STAI; Spielberger, 1983) is a well-known measure of anxiety consisting of scales for state (STAI-S) and trait-level anxiety (STAI-T). Each scale contains 20 items rated on a four-point scale (subscale scores ranging from 20–80). Scores above 40 on each subscale indicate clinical presence of anxiety symptoms. The measure has shown good reliability (Cronbach's α ranging from 0.83–0.86) and discriminant validity (Quek et al., 2004).

Secondary measures

Existential distress. The Death Anxiety Scale (DAS; Templer, 1970) is a 15-item measure that has been used most frequently to assess death anxiety. Items are scored "true" and "false" and then scored as one and zero, respectively. Total scores range between 0–15. Higher scores represent increased severity of death anxiety. Scores below eight are considered normative levels of death anxiety. Templer (1970) reported adequate test-retest reliability (r=0.83) and validity.

The Hopelessness Assessment in Illness (HAI; Rosenfeld et al., 2011) is an eight-item instrument developed for use in patients with advanced cancer. Total scores range from 0–16. Higher scores indicate higher levels of hopelessness. Data have not been published regarding recommended clinical cutoff scores for this measure. This measure has shown adequate internal consistency (Cronbach's α=0.87) and concurrent validity (r=0.70–0.78; Rosenfeld et al., 2011).

The Demoralization Scale (DS; Kissane et al., 2004) is a 24-item questionnaire measuring existential distress encompassing five factors. These dimensions include loss of meaning, despair, disheartened feelings, helpless feelings, and a sense of failure. Likert scale items range from 0–4, and total scores range from 0–96. Score above 30 are considered indicative of clinical levels of demoralization. This measure has shown good reliability (Cronbach's α ranging from 0.71–0.89) and concurrent validity, with regard to related scales (Kissane et al. 2004).

Quality of life. The World Health Organization Quality of Life-Brief Version (WHOQOL-BREF; World Health Organization, 1994) is a 26-item measure providing a broad measure of quality of life across four domains: physical health, psychological health, social relationships, and environment. Likert scale items range from 1–5, and total scores from each of the four domains range from 4–20. There are no published cutoff scores above which quality of life may be considered adequate. This measure has shown good reliability (Cronbach's α ranging from 0.68–0.85) and has been well validated (Oliveira et al. 2016).

Spirituality. The Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being (FACIT-Sp-12; Bredle et al., 2011) is a 12-item measure of spiritual well-being among individuals with cancer and other forms of chronic illness. Items are rated on a five-point Likert scale. The measure yields three subscales: a sense of meaning/peace in life, a sense of comfort from one's faith, and total spiritual well-being score. Total scores for each subscale range from 0–32, 0–16, and 0–48, respectively. Data have not been published regarding recommended cutoff scores for this measure. This measure has shown good reliability (Cronbach's α ranging from 0.81–0.88) and has been well validated (Bredle et al. 2011).

Persisting effects of psilocybin. The Persisting Effects Questionnaire (Griffiths et al., 2006, 2008) assesses self-rated changes in one's attitude, mood, behavior, and experience of spirituality. This measure can detect longitudinal effects of psilocybin administration. An 89-item version was administered to participants in the parent study. In the present LTFU study, the following four questions were drawn from the original version. Participants were asked to indicate: (a) the personal meaningfulness of the psilocybin experience (rated from 1–8, with 1=no more than routine every-day experiences; 7=among the five most meaningful experiences of my life; and 8=the single most meaningful experience of my life); (b) the degree to which the experience was spiritually significant (rated from 1–6, 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); (c) whether the experience and their contemplation of that experience led to changes in their current sense of personal well-being or life satisfaction (rated from +3=increased very much; +2=increased moderately; +1=increased slightly, 0=no change, −1=decreased slightly, −2=decreased moderately, and −3=decreased very much; (d) and the degree to which their behaviors have changed positively as a result of the experience (rated from 0=none, 1=so slight cannot decide, 2=slight, 3=moderate, 4=strong, and 5=extreme).

Mystical experience. Mystical Experience Questionnaire (MEQ-30; MacLean et al., 2012) is a 30-item self-report questionnaire that measures qualities of mystical-type experiences occasioned by a psychedelic. The scale comprises four subscales: "Mystical" factor, "Transcendence of time and space," "Positive mood," and "Ineffability." Items are measured on a six-point Likert scale ranging from zero (not at all) to six (extremely, more than any other time in my life). Total scores range from 30–180. This measure has shown good reliability (Cronbach's α ranging from 0.80–0.93) and has been well validated (MacLean et al. 2012).

Data analysis

Regarding all analyses for both the primary and secondary outcome assessments, both the psilocybin-first and niacin-first dose sequence groups were collapsed and combined into one group. Reasons for this decision included the crossover design, which prevented valid between-group comparisons subsequent to the crossover, and a need to increase power given the modest sample size. The long-terms effects of psilocybin on variables of interest were evaluated using four repeated measures regressions, estimated within the mixed effect repeated measurement (MMRM) model. Planned within-subject t-tests (Tukey's post-hoc) were conducted comparing scores at baseline to the following time points for primary and secondary outcomes: 6.5 months after the second medication session, and the first and second LTFU points. Planned within-subject t-tests were also conducted comparing scores at parent study endpoint (6.5 months) to the two LTFU points. Remissions status (partial or complete remission versus an active diagnosis of cancer) was entered as a covariate into the MMRM model to examine whether it significantly impacted symptomatology on primary and secondary outcome measures.

Rates of clinically significant responses and symptom remission were calculated for primary outcome measures that have empirical support in defining antidepressant (HADS-D, BDI) or anxiolytic response (HADS-A) for each of the dose-sequence groups. Clinical significance was defined as 50% or greater reduction in a score at a particular assessment point relative to baseline (Rush et al., 2006). Antidepressant symptom remission was defined as 50% or greater reduction in depressive symptoms in addition to HADS-D$\leqslant$7 (Hung et al., 2012) or BDI$\leqslant$12 (Reeves et al., 2012; Riedel et al., 2010).

Participants were asked to reflect on their psilocybin session and to rate persisting effects attributed to the medication sessions on four items on the Persisting Effects Questinnaire at the second LTFU: positive behavioral change, meaningfulness, spiritual

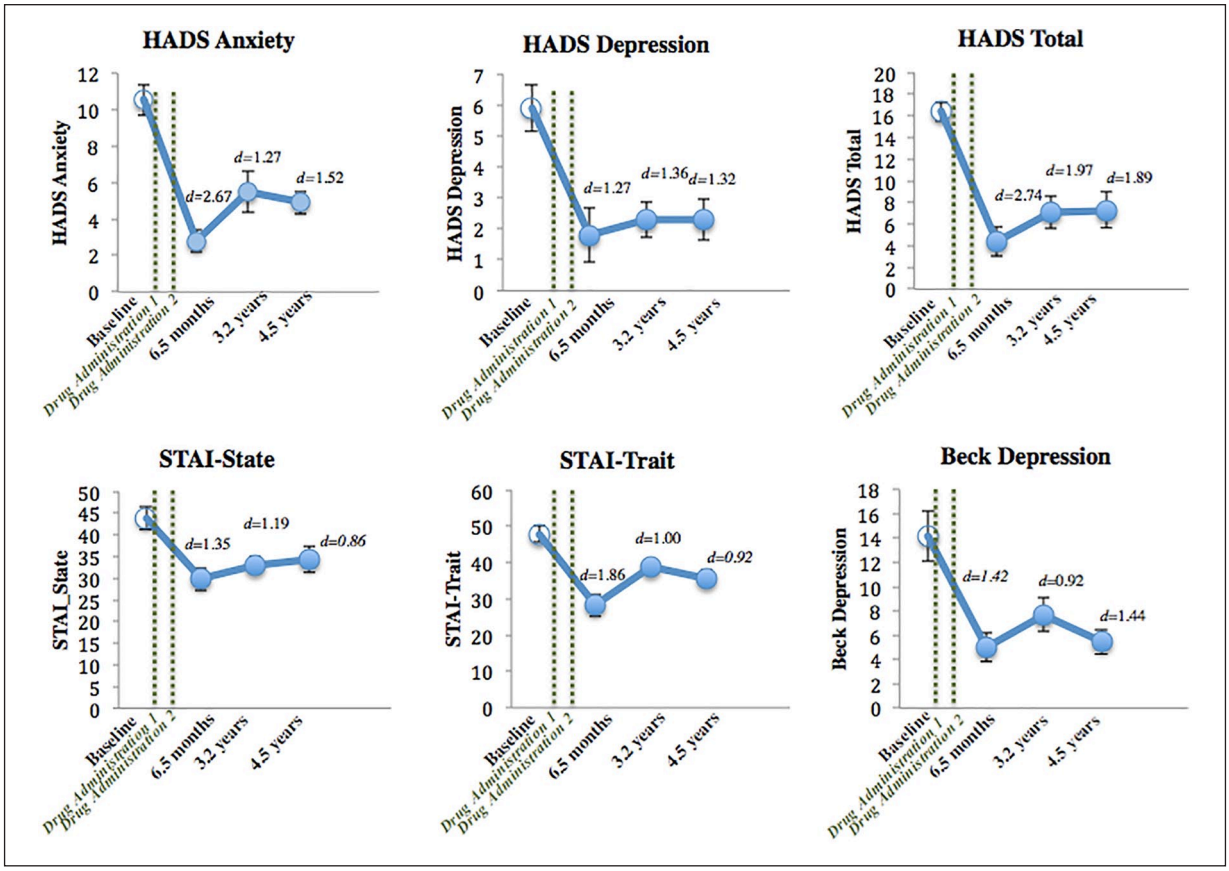

Figure 1. Primary outcome variables: cancer-related anxiety and depression (post-crossover).
Means (±standard error (SE)) for primary outcome measures for both dose-sequence groups combined are shown at the following time points: Baseline (N=16), 6.5 months (parent study endpoint; N=16), mean 3.2 years (first follow-up; N=15), and mean 4.5 years (second follow-up; N=14). Closed points represent significant within-subject differences relative to scores at baseline. Longitudinal within-subject effect sizes, represented as Cohen's d, are shown above time points. HADS: Hospital Anxiety and Depression Scale; STAI: State-Trait Anxiety Inventory.

significance, and increases in personal well-being. Ratings of these persisting effects were expressed as proportions.

Spearman rank correlation coefficients (for use in nonparametric tests) were calculated between total scores on the MEQ-30 assessed at the end of their psilocybin session days and change scores on primary and secondary measures between baseline and the second LTFU assessment.

To determine whether length of time between participants' psilocybin session and the LTFU predicted long-term clinical change, Spearman rank correlation coefficients were calculated between change scores on measures of anxiety, depression, and existential distress (i.e. second LTFU subtracted from two-weeks post-psilocybin) and the total number of days elapsed between each participant's unique individual psilocybin session and the date of their second LTFU assessment. Of note, the range of two-weeks post-psilocybin dose in comparison to the final long-term outcome was selected because the two-week post-dose assessment was the first LTFU point that included all primary and secondary measures.

Results

Primary outcomes

Results of MMRM analyses indicated sustained reductions at the first LTFU point since the final parent study (6.5-month) time point on all primary measures except the HADS-A and STAI-T. Analyses indicated statistically significant reductions relative to baseline on all of the primary measures measuring anxiety and depression at the 6.5-month, first and second LTFU points (see Figure 1 and Table 2). This represented large, statistically significant reductions in symptoms since baseline at the 6.5-month point (mean Cohen's d=1.90, range 1.27–2.67), first LTFU (mean Cohen's d=1.30, range 0.93–1.97), and second LTFU point (mean Cohen's d=1.41, range 0.86–1.89).

At the second LTFU point, 57% of participants showed a clinically significant anxiolytic response on the HADS-A. Seventy-one percent of participants reported clinically significant reductions in global psychological distress on the HADS-T, measuring anxiety and depression combined. Lastly, percentages of clinical responses for depression on the HADS-D and BDI ranged from 57–79%, and depression symptom remission rates ranged from 50–79% at the second LTFU (see Figure 2).

Secondary outcomes

There were significant reductions in hopelessness, demoralization and death anxiety at the 6.5-month, first and second LTFU points relative to baseline. These represented large, statistically significant reductions in symptoms since baseline at the 6.5-month point (mean Cohen's d=1.39, range 0.88–2.00), first LTFU (mean Cohen's

Table 2. Participant ratings on primary and secondary questionnaires.

Measure	Assessment time point			
	Baseline	6.5–8 months	3.2 years	4.5 years
HADS Anxiety	10.56 (0.93)	2.81 (0.95)[a]	5.50 (0.93)[a]	4.99 (0.98)[a]
HADS Depression	5.88 (0.71)	1.75 (0.73)[a]	2.25 (0.71)[a]	2.30 (0.75)[b]
HADS Total	16.45 (1.32)	4.38 (1.35)[a]	7.13 (1.32)[a]	7.34 (1.39)[a]
STAI State Anxiety	43.94 (2.51)	29.84 (2.58)[a]	33.00 (2.51)[b]	34.41 (2.67)[c]
STAI Trait Anxiety	47.81 (2.24)	28.23 (2.75)[a]	3.84 (2.85)[c]	35.78 (3.02)[b]
Beck Depression	14.19 (1.49)	5.09 (1.54)[a]	7.75 (1.49)[b]	5.45 (1.59)[a]
Demoralization	31.88 (2.61)	16.84 (2.67)[a]	13.29 (2.69)[a]	14.32 (2.76)[a]
Hopelessness	5.75 (0.51)	1.65 (0.52)[a]	2.29 (0.52)[a]	1.65 (0.54)[a]
Death anxiety	8.06 (0.78)	6.09 (0.79)[b]	5.68 (0.79)[b]	5.75 (0.81)[c]
Meaning/peace	19.43 (0.92)	26.34 (0.95)[a]	19.27 (0.95)	20.20 (0.98)
Faith	6.75 (1.32)	9.77 (1.34)[b]	9.31 (1.35)[c]	10.43 (1.37)[b]
Spiritual well-being	55.69 (3.16)	70.58 (3.12)[a]	59.85 (3.24)	65.04 (3.31)[c]
Social relationships	13.91 (0.75)	15.27 (0.76)	15.54 (0.77)	14.67 (0.79)
Environmental health	15.50 (0.53)	16.54 (0.53)[c]	16.72 (0.54)[c]	17.00 (0.55)[c]
Physical health	15.00 (0.69)	16.35 (0.70)[c]	16.33 (0.71)	13.89 (0.73)
Psychological health	13.58 (0.43)	15.70 (0.45)[a]	15.48 (0.45)[b]	14.80 (0.46)

HADS: Hospital Anxiety and Depression Scale; SD: standard deviation; STAI: State-Trait Anxiety Inventory.
Data are means (SDs) collapsed across both dose sequence groups (N=16, N=15, N=15, N=14 at baseline, 6.5 months, mean 3.2 years and mean 4.5 years, respectively). Supercripts indicate significant within-subject differences from baseline to time point ([a]$p<0.001$, [b]$p<0.01$, [c]$p<0.05$).

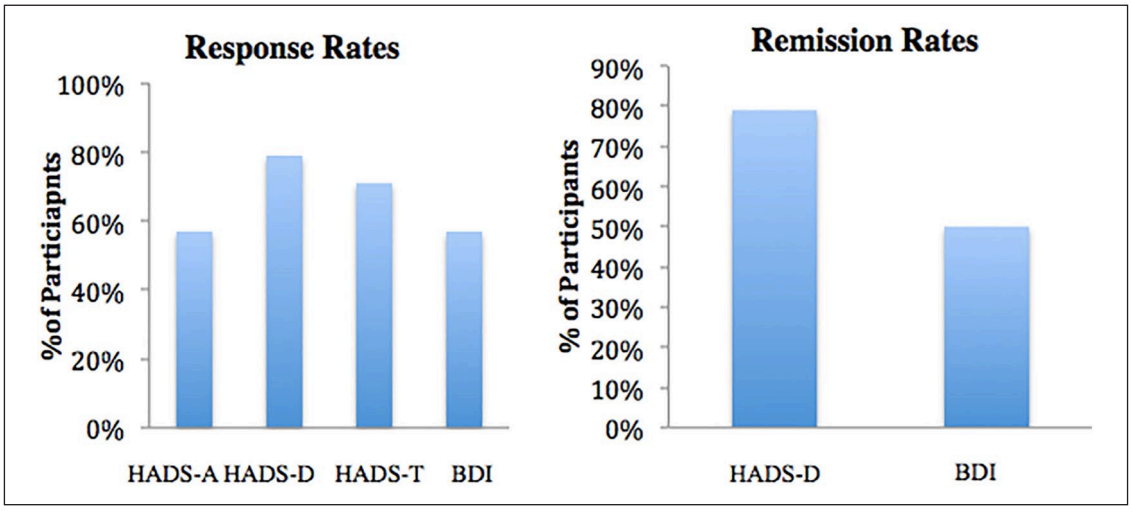

Figure 2. Percentage of participants with antidepressant or anxiolytic response rates and antidepressant symptom remission at final follow-up.
Data are percentages of participants (in both dose sequence groups combined) fulfilling criteria for antidepressant or anxiolytic response or antidepressant symptom remission (Hospital Anxiety and Depression Scale-Depression (HADS-D), Beck Depression Inventory (BDI)) at the 4.5-year point (second long-term follow-up; N=14). Clinical response was defined as 50% or greater decrease in each measure relative to baseline; symptom remission was defined as 50% or greater decrease in the measure relative to baseline and a score of ⩽7 on HADS-D or ⩽12 on BDI.

d=1.39, range 0.80–1.77), and second LTFU (mean Cohen's d=1.60, range 1.00–2.00). Results are presented in Figure 3. There were also significant improvements in spiritual well-being and faith domains (FACIT-Sp-12) at the second LTFU relative to baseline. Results on quality of life were mixed: there were increases on the psychological (i.e. self-esteem and emotional health) and environmental (i.e. financial resources, physical security, participation in recreational activities) dimensions of quality of life at the first LTFU, however, gains in psychological health at the first LTFU were not sustained at the second LTFU.

Mystical-type experience scores (MEQ-30) collected on participant's psilocybin dosing day in the parent study did not significantly correlate with primary outcome LTFU change scores (second long-term LTFU relative to the psilocybin dosing day) on any of the primary outcome measures of anxiety or depression.

Participant ratings of persisting effects are displayed in Figure 4. Participants indicated positive attributions to the psilocybin experience that persisted until the second LTFU. Seventy-one percent of participants continued to rate the psilocybin experience the single or top-five most personally meaningful experience(s) of their lives.

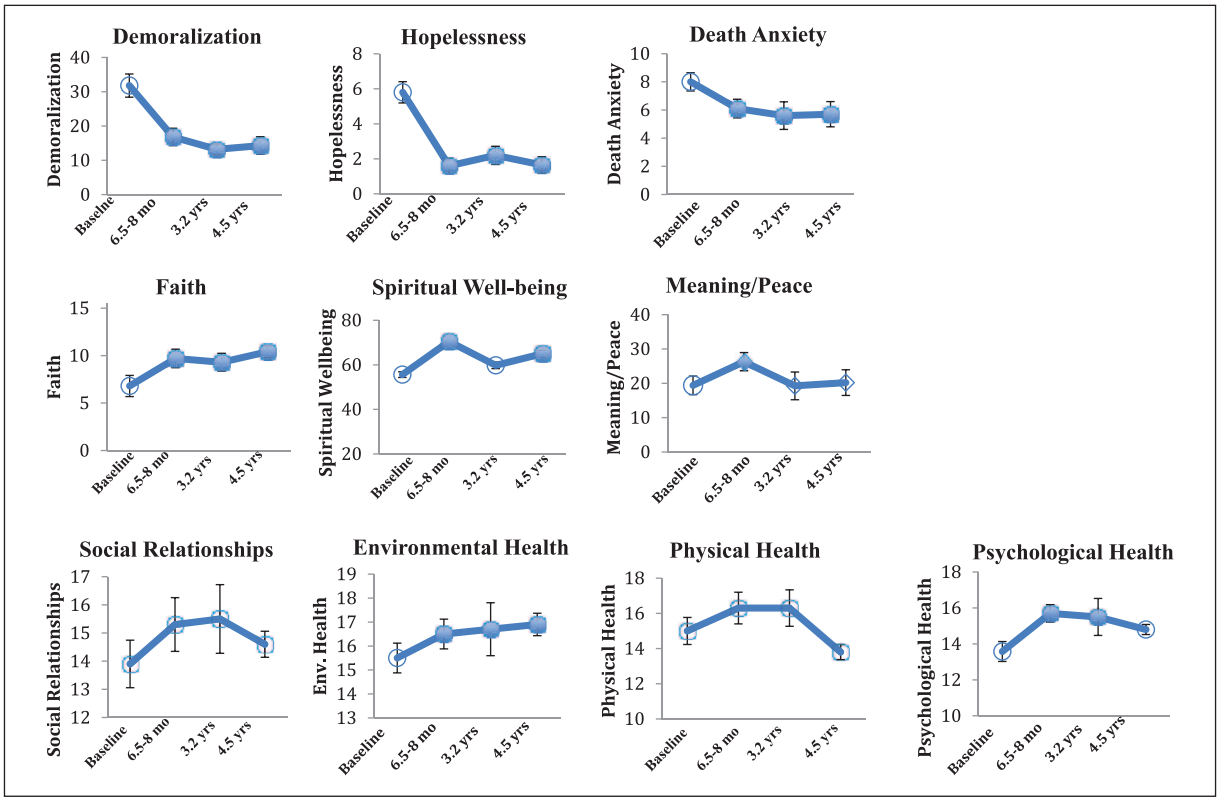

Figure 3. Secondary outcome measures: existential distress, spirituality, and quality of life.
Means (±standard error (SE)) for secondary outcome measures for participants (in both dose sequence groups combined) are shown at the following time points: Baseline (*N*=16), 6.5 months (parent study endpoint; *N*=16), mean 3.2 years (first follow-up; *N*=15), and mean 4.5 years (second follow-up; *N*=14). Closed points represent significant within-subject differences relative to scores at baseline.

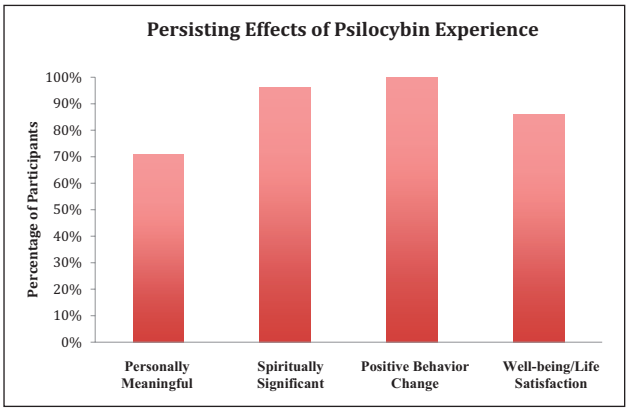

Figure 4. Persisting effects attributed to psilocybin administration.
Percentage of volunteers who endorsed persisting effects attributable to psilocybin administration on the Persisting Effects Questionnaire at the at the 4.5-year point (second long-term follow-up; *N*=14): percentage who endorsed "among the top five" or "the single most" personally meaningful experiences; "among the top five" or "the single most" spiritually significant experiences; "moderate," "strong" or "extreme" positive behavioral change; and "increased moderately" or "increased very much" well-being or life satisfaction.

Ninety-six percent rated the psilocybin experience the single or top-five most spiritually significant experience(s) of their lives. Participants appraised the psilocybin session as increasing life satisfaction or wellbeing at a rate of 86%. Lastly, 100% of volunteers reported "moderate," "strong" or "extreme" positive behavioral change attributed to the psilocybin experience. Cancer remission status (partial or complete remission versus an active diagnosis of cancer) did not significantly interact with any of the scores on primary or secondary outcome measures.

Length of time between psilocybin session and follow-up (i.e. second LTFU relative to each participant's two-week-post-psilocybin dosing date) correlated positively with depression and hopelessness change scores (second LTFU subtracted from two-weeks post-psilocybin dose scores) on the following measures: HAD-D (r=0.70, p<0.01) and HAI (r=0.69, p<0.01). Results are depicted in Figure 5.

Participants were asked open-ended questions about their psilocybin-assisted psychotherapy experience to further understand the enduring high ratings of persisting effects at the second LTFU. Table 3 presents verbatim written comments about the nature of their psilocybin-assisted psychotherapy experiences.

Discussion

This is the first report of long-term effects of psilocybin treatment in patients with cancer-related psychiatric and existential distress at two long-term follow-ups. The data suggest that psilocybin-assisted psychotherapy was associated with large and significant reductions in anxiety, depression, hopelessness, demoralization, and death anxiety, as well as improvements in spiritual well-being at an average of 3.2 and 4.5 years following psilocybin administration, after a

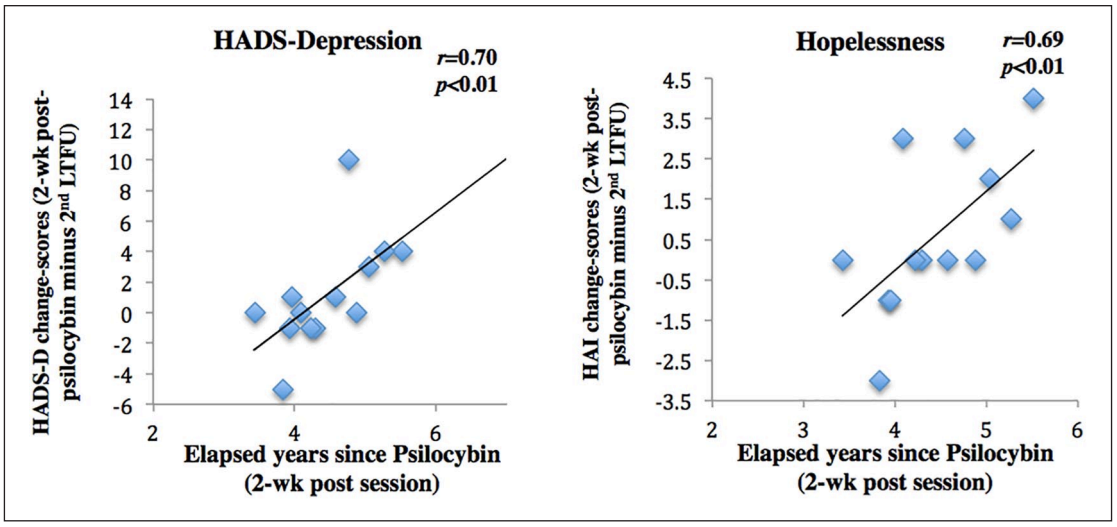

Figure 5. Relationship between time elapsed between psilocybin session and second long-term follow-up, and outcome measures assessed at two weeks after psilocybin session.

Each graph shows scores on an outcome measure assessed two weeks after participants' psilocybin session as a function of elapsed time between the two-week post-psilocybin date and each participant's second long-term follow-up date. Correlation coefficients and *p*-values are displayed. HADS: Hospital Anxiety and Depression Scale; LTFU: long-term follow-up.

Table 3. Verbatim written comments about the nature of the psilocybin experience from participants at the second long-term follow-up (LTFU). These comments were excerpted from a questionnaire that asked open-ended questions about positive changes attributed to the psilocybin-assisted therapy experience.

Volunteer	Verbatim comments
13	I'm more creative in my work and take more chances. I'm back to performing, like I did before. I bring more openness to my art. And connect to others on a more creative level.
14	It has given me a different perspective on my life and has helped me to move on with my life and not focus on the possibility of cancer recurring. I try not to hold onto or stress unimportant things.
15	[I experienced a] greater awareness of a spiritual connection to the universe. . . of the profound beauty of nature.
16	I've always been afraid of rejection. I experienced such overwhelming love in my psilocybin experience, that it gave me new confidence. I threw myself a birthday party and invited more people than I thought I ever could. They came! I think the extreme depth of love I felt changed the way I relate to others. [It] gave me a feeling that I have a right to be here and to enjoy life.
27	It's hard to explain. . . something in me softened, and I realized that everyone is just trying (mostly) to do the best they can. Even me. And that matters, since we are all connected.
28	[I] most certainly feel a stronger connection to a higher power due to the psilocybin experience, [as well as] greater openness towards others, more empathy, more interconnected with other people. I believe these changes are directly attributable to the psilocybin experience as well as the integration sessions afterwards.
34	There's a reckoning, which came with cancer, and this reckoning was enhanced by the psilocybin experience. I have a greater appreciation and sense of gratitude for being alive.
35	Once the thought that cancer is a part of your life becomes woven into the fabric of your being, you realize that this, or something similar, awaits many others who are unsuspecting. This compels you to relate to others from the perspective of compassion due to the changeable and temporary nature of our sense of who we are. Radical change is just around the corner regardless of how certain we are of our current state. We are children in our understanding of life until something reaches into your heart and announces itself. I understand the life process to be one of realization of our divine nature. This does not include any supernatural creature; it is a process of remembrance
36	[The] experience reinforced the understanding that we are all very much together, that [the] prevailing feeling in the end is love.
42	The psilocybin experience changed my thoughts about myself in the world. I see myself in a less limited way. I am more open to life. It has taken me out from under a big load of feelings and past issues in my life that I was carrying around.

crossover. The magnitudes of reductions relative to baseline in primary measures of anxiety and depression were large, with the largest effect sizes seen for global distress of combined anxiety and depression. Approximately 60–80% of participants continued to meet criteria for clinical antidepressant or anxiolytic response and remission at the second LTFU. At the second LTFU, participants overwhelmingly (71–100%) attributed subjective experiences of positive changes to the psilocybin-assisted psychotherapy

experience, reporting improved well-being or life satisfaction, and rating it among the most personally meaningful and spiritually significant experiences of their lives.

Due to the limitations of the crossover design of the parent study, it is not possible to attribute long-term improvements in psychiatric and existential distress directly to psilocybin-assisted psychotherapy. The majority of participants met criteria for an adjustment disorder (on the DSM-IV-TR) relative to cancer-related stressors at enrollment, and 71% reported entering partial or complete cancer remission at the second LTFU. Participants may have thus experienced naturalistic or spontaneous diminishment of distress and resolution of their adjustment disorders as they entered remission and approached the five-year cancer survival threshold. It is also possible that other psychiatric interventions received after the end of the parent trial accounted for improvements in depressive or anxious symptoms. However, this possibility is less likely given that in the follow-up assessment period only 8% of participants reported receiving any psychotherapy or pharmacotherapy specifically targeting cancer-related psychiatric distress.

These findings have meaningful implications for the clinical management of cancer-related existential distress. It is hopeful to consider the possibility that psilocybin-assisted psychotherapy could represent the first empirically-driven pharmacotherapy intervention to treat this indication. Existential distress is under-recognized and under-treated in cancer patients within Western medicine (Cepoiu et al., 2008; Gouveia et al., 2015). Among medical illnesses, depression and hopelessness associated with a diagnosis of cancer can serve as severe stressors and are well-known risk factors for suicidal ideation and completed suicides (Rosenfeld et al., 2011; Breitbart et al., 2000). The potential rapidity and long-term durability of psilocybin-assisted psychotherapy's effects represents a promising protective strategy against suicides. Future trials should carefully explore this application with cancer populations with chronic, passive suicidality, as there is preliminary evidence that psychedelic use may prevent suicidal ideation and behaviors (Hendricks et al., 2015; Johansen and Krebs, 2015).

An intriguing finding from our analyses was that the greater amount of time that had passed between participants' psilocybin session and the second LTFU predicted stronger reductions in subjective reports of depression and hopelessness during this period. The significance of this finding is unclear. However, it is interesting to consider that certain domains of cancer-related distress, particularly certain key domains of existential distress, could continue to improve rather than diminish over time in relation to a single psilocybin session. The extended follow-up is an important strength of this study as the vast majority of psycho-oncology RCTs to treat psychological distress report a follow-up period of typically no more than one year following treatment (Faller et al., 2013; Gasser et al., 2015; Stagl et al., 2015)

If it were established that psilocybin-assisted psychotherapy effectively treats cancer-related psychiatric and existential distress, it would be important to understand the neurobiological and psychological mechanisms of action. In our previous report, the psilocybin-facilitated mystical-type experience was found to partially mediate the effect of dose sequence on anxiolytic and antidepressant effects of psilocybin-assisted psychotherapy prior to the crossover, suggesting that acute aspects of participants' subjective experience may explain changes in psychiatric outcomes up to seven weeks (Ross et al., 2016). In the present study, a mystical-type experience was not associated with long-term changes at the LTFU points. A reduction in power might have weakened our ability to detect an effect as the sample size in this LTFU study was reduced by 50%. It is also possible that the mystical-type experience does not represent a significant psychological change mechanism accounting for psilocybin's therapeutic effects, or that other aspects of participants' experiences are more influential in determining longer-term response. However, given the growing body of evidence linking the intensity of the psilocybin-facilitated mystical-type experience to therapeutic improvements across a range of psychiatric and addictive disorders (Bogenschutz et al., 2015; Garcia-Romeu et al., 2014; Griffiths et al., 2016; Pahnke et al., 1969; Roseman et al., 2019; Ross et al., 2016), it is important to further explore this potential psychological mechanism of action in additional adequately-powered RCTs. It would also be important to explore other potential psychological change mechanisms of psilocybin-assisted psychotherapy in this patient population.

One such mechanism may relate to rapid and enduring shifts in cognition. Classic psychedelics offer a rapid means of dismantling habitual mental templates that, over time, may rigidify one's attention and behavior—patterns that are associated with various psychiatric pathologies (Carhart-Harris, 2018; Carhart-Harris and Friston, 2019). Psychedelic-induced states of consciousness are, instead, associated with increases in trait openness and cognitive flexibility (Carhart-Harris et al., 2012; Kuypers et al., 2016). In an open-label trial of psilocybin in patients with treatment-resistant depression participants reported increased trait openness, with significant increases in the following sub-traits: "openness to values" (i.e. valuing open-mindedness and psychological flexibility) and "openness to actions" (i.e. readiness to try and engage in new activities; Erritzoe et al., 2018). Being open to novel and more constructive ways of thinking, feeling and behaving is one of the central goals of contemporary evidence-based psychotherapies (e.g. cognitive behavioral therapy and Acceptance Commitment Therapy (Hayes et al., 2012)), and enhanced cognitive and psychological flexibility may constitute a psychological mechanism mediating psilocybin-assisted psychotherapy's antidepressant and anxiolytic effects (Watts and Luoma, 2020). Further, given the link between enhanced mystical-type states and enduring increases in trait openness (MacLean et al., 2011), it is possible that certain features of the mystical-type state (e.g. dissolution of boundaries and feelings of unity) lead one to develop enduring increases in psychological flexibility when coupled with supportive psychotherapy. The psilocybin experience may have enabled participants to establish a new inner framework from which they could flexibly avail themselves of resources internally and in their environment to cope with life stressors, particularly stressors associated with their cancer diagnoses.

It is also possible that other aspects of the acute psilocybin experience, such as challenging (Barrett et al., 2016) or emotional breakthrough experiences (Roseman et al., 2019), are more influential in explaining long-term changes of psilocybin-assisted psychotherapy. The resolution and integration of difficult emotions may be particularly relevant for clinical populations such as cancer patients, and such emotional processing may support the development of greater psychological flexibility and emotional regulation in the long-term (Lane et al., 2015). It would be important to assess these potential psychological change mechanisms

in future trials that are adequately designed and powered. These theories are supported by a growing consensus that serotonin 2A signaling mediates functional shifts in connectivity in cortico-striato-thalmo-cortical pathways (Preller et al., 2019), increased entropy in the brain (Carhart-Harris, 2018), and disruption of activity within the default mode network, a brain system that is associated with self-referential information processing and mind-wandering (Carhart-Harris and Nutt, 2017; Carhart-Harris and Goodwin, 2017; Ly et al., 2018). These theories are also consistent with the quantitative (Ross et al., 2016) and qualitative (Belser et al., 2017; Swift et al., 2017) findings from the parent trial and the present study of highly memorable, meaningful, and spiritually significant effects attributed to the psilocybin experience. We strongly believe, however, that an isolated experience with psilocybin does not inherently confer therapeutic benefits. Rather, the development of an enduring therapeutic experience is contingent on contextual factors, such as the presence of skilled therapists or guides, which facilitate a larger psychotherapeutic process. It is, therefore, important to recognize that purely neurobiological interpretations regarding brain activity during acute phases of a psilocybin experience will not adequately capture the dynamics of a psychotherapeutic process that may unfold in the weeks or months thereafter, fostering enhanced meaning and greater well-being.

Limitations

There were several limitations of this study, which suggest directions for future research. The use of a crossover design in the parent study at seven weeks permitted an assessment of acute and enduring effects among both dosesequence groups combined but does not enable a true control group for comparison after seven weeks. It is also not possible to separate the effects of the psilocybin medication from those of the psychotherapeutic session and context into which the medication session was embedded. Additionally, the small number of participants participating in this follow-up reduces statistical power, which could increase the effect of outliers on outcomes, and affects generalizability of the findings. Further, the sample was not ethnically, racially or socioeconomically representative of cancer patients in the USA (e.g. 94% of the sample was non-Hispanic Caucasian, and 86% were well-educated and from higher socioeconomic backgrounds), which substantially limits the generalizability of our findings to other cultural groups. Across modern trials of psychedelic-assisted therapies, minority groups are greatly underrepresented, and future investigators should make concerted efforts to address this issue by developing research-community collaborations to decrease prohibitive barriers to participation (George et al., 2019; Michaels et al., 2018). Future studies should also endeavor to include a larger sample of participants with a placebo-control group, without a crossover, to establish a more rigorous experimental design.

Conclusion

In summary, the findings of this LTFU study represent the first suggestion of persistent long-term effects of psilocybin-assisted psychotherapy for cancer-related distress. Although limited conclusions can be drawn regarding efficacy due to the crossover design, results suggests that the treatment continues to be associated with reductions in anxiety, depression, hopelessness, demoralization, and death anxiety up to an average of 4.5 years following a single psilocybin session in conjunction with psychotherapy. Theories regarding neurobiological and psychological change mechanisms remain speculative and exploratory. Further research will need to validate the main findings of the parent trial and this LTFU article with a fully experimental design in order to empirically establish the use of psilocybin-assisted psychotherapy to treat the psychiatric and existential distress of those with life-threatening cancer diagnoses.

An advanced experimental design of psilocybin-assisted psychotherapy would likely include a larger sample size (i.e. N=200) that is nationally representative of cancer patients. It would also include randomized, parallel groups without a crossover, use of an adequate placebo control group, measures taken to minimize blinding and expectancy effects, and the use of valid and reliable outcome measures. It might also include design elements that would allow for exploration of potential neurobiological (e.g. growth factor expression, functional connectivity, neuroplasticity) and psychological (e.g. mystical experience, personality, psychological flexibility, emotional breakthroughs and insights, challenging experiences) mechanisms of action of psilocybin-assisted therapy.

Funding for psychedelic research in the USA remains mostly limited to the private sector at present time. It would be an historic and important milestone if the National Institutes of Health were to fund advanced research exploring the therapeutic potential of psilocybin-assisted psychotherapy in patients with life-threatening cancer and concomitant psychiatric and existential distress. If the Food and Drug Administration were to sanction this next phase of research (i.e. phase III trials) for this clinical indication, and favorable findings were to emerge, it could help to form a pathway for psilocybin to become re-scheduled and clinically available for cancer patients. It would represent a major paradigm shift in the psycho-oncological approach and care of patients with cancer. The use of psilocybin-assisted psychotherapy for those with life-threatening cancer could be especially useful in helping patients approach their lives with enhanced psychological, emotional, and spiritual wellbeing.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The Source Research Foundation provided Gabrielle Agin-Liebes a grant for the long-term follow-up study. The parent study research was supported by grants from the Heffter Research Institute, the RiverStyx Foundation, and the New York University-Health and Hospitals Corporation (NYU-HHC) Clinical and Translational Science Institute (CTSI) (NYU CTSA grant UL1 TR000038 from the National Center for Advancing Translational Sciences, National Institutes of Health). Funding for the trial was also provided by William Linton, Carey and Claudia Turnbull, and Efrem Nulman. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of this manuscript. Trial Registration: clinicaltrials.gov Identifier: NCT00957359.

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